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THE WILLIAM HENRY WELCH LECTURES

I. STUDIES ON THE DEHEPATIZED ANIMAL. A REVIEW*

FRANK C. MANN, M.D.

[Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota]

The history of development of physiology indicates that the evaluation of the physiologic importance of the liver has undergone wide fluctuations extending over long periods. It would appear that in ancient times, probably because of its large size, the organ was considered to be of very great importance, even to the extent of being regarded as the seat of the life processes. It was early recognized that the liver gave origin to the yellow bile and the production of heat and many other less defined activities were attributed to it. Evidently the ancient observers of the animal organisms and mechanisms of life considered the functions of the liver to extend beyond the confines of the organ itself.

This concept of the importance of the liver was pushed into the background by the introduction of the experimental method of research and the great anatomic and physiologic discoveries made at this same time. The methods available at this period were not suitable for the investigation of the functions of the liver except in regard to the secretion of bile but were applicable for investigation of the vascular and other systems. The resulting discoveries were so great and attracted so much interest that for a period of almost two centuries the liver was considered of little more importance than an organ for the secretion of bile.

However, methods, rather crude in comparison with those of the present day, were developed which could be used to investigate the functions of the liver and the physiologists were awakened from their lethargy in regard to the organ with startling suddenness by the epoch-making discovery of the liver glycogen and formation of sugar from it by Claude Bernard (1), who can rightly be called the father of hepatic physiology. His discoveries created a new wave of interest in the functions of this great organ which persisted for almost half a century. While the number of facts discovered concerning hepatic activity during this period of time was rather meager their implications were great and gave rise to hypotheses and speculations which have required almost another half century of intensive research to prove or disprove.

The story of the discoveries of the present known functions of the liver affords an excellent illustration of the fact that the growth of physiologic knowledge depends in such a great measure upon the experimental method and the development of technics for quantitation. The conclusion of the early observers that the liver is of great importance was based upon the anatomic and physical characteristics of the organ which they could perceive with their own senses.

* Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, New York, April 3, 1944.

Later when methods became available for the study and measurements of the circulation and other physiologic mechanisms, the evaluation of the liver decreased because discovery of most of its functions require more subtle methods. While the biochemists have at times greatly befuddled the physiologic concepts regarding the liver by making only partially correct deductions concerning their chemical data, they have been the most important group in making it possible to advance the knowledge of the functions of the organ by the development of quantitative methods for the various constituents of the blood, secretions, tissues of the body and so forth. Without this aid current knowledge of the liver in health and disease would be much less than it is.

Several years ago, at the suggestion of colleagues, friends and publishers, I rashly undertook to write a book on the functions of the liver. It soon became apparent that too many gaps existed in knowledge of the physiology of the liver to justify a book on the subject. At a later period I again took up the task and again quit, not only because of lack of exact knowledge of so many phases of hepatic function but also because of deficiencies in knowledge concerning anhepatic physiologic activities in which the liver had a part.

My meaning can be illustrated in the following manner. If one leafs through the index of the current textbooks on physiology, one notes that whereas most of the pages indexed under organs such as the kidney, heart and so forth are for the most part consecutive, those found under the heading "liver" are distributed throughout the book. Many texts of physiology do not have a chapter devoted to the liver and the subject material of the chapters on the liver, when they are present, deals almost exclusively with the secretion of bile with occasionally, in addition, a short abstract of the major functions of the organ. Thus the books on physiology indicate quite clearly that many of the known functions of the liver are, as the ancients appear to have deduced from their observations, but part of physiologic processes involving other organs and tissues of the body. Understanding of the hepatic phase of a physiologic process often depends upon exact knowledge of the anhepatic phases.

What method then can be used to investigate the functions of an organ, like the liver, whose activities involve so many, so varied and so widespread physiologic mechanisms? It is obvious that no one method will suffice. The functions of the liver can best be discovered by the use of many methods and by attempts to develop the story of its activities by correlating the data obtained by such diverse means of investigation. Such a program for investigating the functions of the liver has been in progress in many laboratories and clinics for the past quarter of a century and the combined results of the investigations have amply confirmed the ancient view that the liver is a very important organ.

In this lecture I wish to present a brief review of the results obtained by the use of one method of investigation of the functions of the liver, total ablation of the organ. While the subject material will consist preponderantly of a presentation of data and a discussion of the problems of hepatic physiology in which my associates and I have had the most interest, I shall attempt to present a fairly complete summary of the more important facts that have been learned by studies

on the dehepatized animal. It should be noted that such studies, in order to be successful, require the co-operation of a number of workers to an unusual extent. In this respect our laboratory has been very fortunate and several persons have participated in developing the story of the dehepatized animal as colleagues of Magath, Bollman and myself.

It is unnecessary to discuss the value and limitations of the method of determining the functions of an organ by studies on the effects produced by its total removal. Suffice to emphasize that, as in the use of any method of investigation, cognizance should be given to the limitations of the conclusions that can be made in regard to the effects of removal of an organ. In this review I shall attempt to present a picture of the sequence of events that occur in an organism after the total removal of the liver. You are all familiar with the more discernible of these events which have formed the basis of positive conclusions in regard to hepatic activities. There are several less easily elicited reactions occurring in the liverless animal concerning which conclusions cannot at present be made. These unexplained reactions often appear to be anhepatic to a considerable extent and emphasize the fact that the liver usually plays but a part in physiologic processes which involve the whole organism. It is the problems associated with the latter that I wish to emphasize.

My desire to develop a method for the removal of the liver from an otherwise intact animal of the higher species, as the dog, was stimulated by reading the case report of a human being in which the pathologist stated that the only hepatic tissue present consisted of small fibrotic remnants. The history and pathologic findings in this case gave rise to the thought that if a human being could live with such a small amount of hepatic tissue it might be possible for an animal to live without any liver tissue. The logical question was raised that possibly the liver, in spite of its large size, was not as important physiologically as had been surmised.

It is unnecessary to give details of technics and methods for total removal of the liver because several satisfactory methods are available to the investigator at the present time (2, 3, 4, 5). However, any method for the removal of the liver must obviate two possible sources of error if the liverless animal is to be studied successfully for any great length of time. The organ must be totally removed from the body. A very small amount of hepatic tissue with intact blood supply may maintain some of the functions of the liver for many hours, as in the case of the frog and fish, in which species a definite small portion of the organ is very difficult to remove and even days may elapse before typical symptoms and findings indicating hepatic insufficiency ensue. If the remaining hepatic tissue lacks an adequate blood supply, toxic symptoms which differ in several respects from those of acute hepatic insufficiency and which lead to a rapid, fatal outcome develop. This complicating result occurs most frequently in the dog and is owing to the products of autolysis of the hepatic tissue which is usually aided by bacterial activity. The removal of the organ must not cause an inadequacy of the return of venous blood from the viscera and lower extremities. Venous stagnation, particularly in the viscera, greatly modifies the course

of events that occurs in the dehepatized animal. Finally it should be emphasized that in order for the resulting data to be accurate and worth while the technic of removal of the liver must insure a normal appearing and acting animal at the conclusion of the operation and recovery from anesthesia.

The liver was successfully removed in the second animal in our series in which the operation was attempted and when I viewed the dog five hours later at a time when it appeared normal, walking around, responding to call and commands, drinking milk and so forth, I felt that possibly my deduction from the history of the case of the human being, that the animal organism could survive without a liver, might be correct. However, my elation over this outcome did not survive the sixth hour after completion of the operation because a group of symptoms with which I was not familiar developed and the animal died in coma.

After we had observed the course of events in several dehepatized animals we attempted to determine what was occurring to cause the characteristic symptoms and death. Data on the pulse, respiration, blood pressure and temperature did not aid in this respect. We turned to investigate the various constituents of the blood and soon noted that the concentration of sugar in the blood always decreased and that the development of the symptoms appeared to bear a relation to the hypoglycemia (6). The work of Bernard and a few succeeding investigators had prepared us for the finding of a decreased blood sugar in the liverless animal but the development of the concomitant characteristic symptoms came as a surprise.

I think it can safely be said that the decrease of blood sugar and, to a lesser extent, the concomitant development of the characteristic symptoms associated with the hypoglycemia that occurs in the dehepatized animal constitute one of the most constant of biologic phenomena. The liver has been removed from hundreds of animals, including representatives of several species, but in no instance has the blood sugar failed to decrease. No experimental condition has yet been devised in which loss of the liver was not followed by a decrease of the sugar of the blood except as a result of the administration of glucose or substances from which glucose could readily be made within the liverless body. This fact would appear to prove conclusively that a minimal amount of glucose is required and is constantly being utilized in some manner by the animal organism during life. I think this fact is so uncontrovertible and important that it can never be ignored in any consideration of the metabolism of carbohydrate in either health or disease.

It has been a well-known fact for many years that glycogen is found in many tissues of the body besides the liver and that the total amount of glycogen in the muscles exceeds the amount in the liver. As a next step in our investigation it was logical to determine if this large source of glucose from the muscle had been used to maintain the blood sugar after removal of the liver. We found that whereas the glycogen content of the muscle was always decreased after hepatectomy in comparison with the amount present before operation, there was always a sufficient amount of glycogen remaining in the muscles to have maintained the blood sugar level for a considerable time if it had been available for this

purpose (7). Evidently the glycogen in the muscle cannot be utilized for maintaining the glucose concentration of the blood. The results of recent investigations have suggested the cause for this but its significance that the liver is the sole or main source of the sugar in the blood has probably not been emphasized sufficiently.

Little can be stated positively in regard to the glycogen found in the other tissues of the body, notably brain, kidney and mammary gland, in relation to the maintenance of the blood sugar. The evidence would indicate that such stores of carbohydrate are utilized for other purposes than supplying glucose to the blood, such as the formation of lactose from the glycogen in the secreting mammary gland (8). At any event the total amount of glycogen normally found in the tissues of the body other than liver and muscle is small and even if it could be added to the blood, it would contribute only a small part of the total amount required for keeping the concentration of the sugar in the blood at normal values. While it cannot be stated that the extrahepatic glycogen does not give rise directly to glucose in the blood, the evidence in favor of such an occurrence is meager.

After the relationship of the decrease of blood sugar to development of symptoms became apparent, the next logical step was to determine if the administration of glucose would be of benefit. I definitely recall the hot afternoon on the last day of August in 1920 when this question received an answer. The blood sugar concentration in the dehepatized animal had decreased in the usual manner; the animal was flaccid and unable to stand. An injection of 40 c.c. of a 10 per cent solution of glucose was begun. Before the solution was more than three-fourths injected, to our amazement the animal suddenly arose and jumped off the table. Our question had been answered in an unbelievable and startling manner.

It was now pertinent to determine if the resuscitation of the hypoglycemic liverless animal by glucose was specific for this substance or whether other substances were equally or partially effective. Our first efforts were limited to two groups of substances: (1) those which might alter the osmotic state of the blood and tissues and (2) those which had been considered intermediary products of glucose metabolism. Later a wide variety of substances were injected into the hypoglycemic animals. The results of these experiments were very definite and conclusive. The dehepatized animal in hypoglycemia was restored to normal only by glucose or substances from which glucose could be made. Evidently glucose was a specific agent for restoration of the hypoglycemic animal (9). This conclusion has been amply confirmed by other investigators, using either the dehepatized (10, 11) or eviscerated animal (12) or insulin (13) to produce hypoglycemia.

One of the substances, fructose, used as a substitute for glucose in the dehepatized animal caused us considerable difficulty. It was readily determined that the injection of fructose into the liverless animal in a condition of hypoglycemia was ineffectual and the animal would die without recovery from the hypoglycemia unless glucose was administered. The amount of glucose injected which caused restoration was much smaller than the amount of fructose

administered which had been without benefit. Later we found that if the dehepatized animals were injected with suitable amounts of fructose before the extreme stage of hypoglycemia had been permitted to develop, the animals remained normal. Determinations of the glucose and fructose content of the blood in this group of animals showed that the amount of glucose increased at the expense of the fructose.

In an attempt to determine the extrahepatic site of conversion of fructose to glucose we removed all the abdominal viscera at the time the liver was removed. To our surprise fructose was found to be ineffectual in preventing hypoglycemia and death in eviscerated animals. Furthermore, the injection of fructose was not followed by an increase of blood glucose. We then removed various organs at the same time that the liver was removed in order to determine more definitely the site of formation of glucose from fructose. The process was found to be present following the removal of the liver with pancreas, kidney and spleen but was absent when the gastro-intestinal tract was removed with the liver (14).

Our results in regard to the utilization of fructose in the absence of the liver have been confirmed but the conversion of fructose to glucose in the presence of the gastro-intestinal tract has been questioned. Drury and Salter (11), in a study of glucose derivatives upon the survival time of dehepatized rabbits, found that fructose was about half as effective as glucose in preventing the prostration associated with hypoglycemia. Griffiths and Waters (15) found that the mammalian organism could use fructose in the absence of the liver. They also concluded that the eviscerated animal could assimilate fructose and that fructose was not converted to glucose in the dehepatized or eviscerated animal. Maddock and his associates (12) ingeniously used the characteristic electro-encephalogram of hypoglycemia as an indication of the effectiveness of several different substances to restore the hypoglycemic animal. They found that fructose was without effect on the electro-encephalogram of the eviscerated animal in hypoglycemia, although glucose restored the animal to normal.

Corkill and Nelson (16) infused fructose by single or constant injection into spinal eviscerated cat preparations and determined the fructose content of blood and muscle. They found that (1) with a constant rate of infusion the concentration of fructose in the blood steadily increased and insulin did not in any way influence this phenomenon, (2) formation of lactic acid did not appear to be of great importance in the intermediate metabolism of fructose, and (3) almost all the injected fructose was found in the blood and muscles. They concluded that fructose, as such, is not utilized to any appreciable extent by the peripheral tissues.

Reinecke (17) used the rat in his studies. He concluded that the eviscerated, nephrectomized rat can destroy fructose and that fructose would prolong the life of the eviscerated, non-nephrectomized rat. It should be noted that the average length of life after evisceration in the animals given fructose in this series of experiments was slightly less than the average length of life in another series of experiments made by the same investigator in which only saline solution

was given (18). The results of other methods of investigation of this problem made by different investigators have also been contradictory. It is apparent that more work is necessary before an agreement can be reached in regard to the site and manner of utilization of fructose in the absence of the liver.

Removal of the liver greatly reduces the utilization of galactose but a small amount of the galactose injected into the liverless animal cannot be found in the blood and urine, indicating utilization in some manner (19). It is surprising that this sugar, which is the sole source of carbohydrate for the newborn animal, should apparently be utilized with such great difficulty by the adult animal.

One of the first questions for which we attempted to find an answer after we had discovered the specific effect of glucose in restoring the hypoglycemic dehepatized animal was, What is the amount of glucose which will prevent hypoglycemia from occurring in the liverless animal? At that time we had the idea that if we could find the amount of glucose that would prevent hypoglycemia after removal of the liver we could calculate approximately the amount of glucose the liver was normally adding to the blood stream. We found that a single injection of 0.25 gm. of glucose per kilogram of body weight would maintain the blood sugar of a liverless animal for approximately one hour and that if 0.25 gm. of glucose per kilogram of body weight per hour were injected continuously the blood sugar would remain within normal limits for several hours after operation (9). Soskin and his associates (20) have obtained this same value in dogs. The finding that the administration of 0.25 gm. of glucose per kilogram of body weight maintained the blood sugar level of a dehepatized dog within the normal limits for the first few hours after removal of the liver has been so consistent and has been noted in such a large number of animals that I believe it is significant in this respect: it indicates that under the standard conditions of our experiment and at the normal blood sugar level approximately that amount of glucose was normally leaving the blood stream in this species. In all probability a lesser amount of glucose disappears following the removal of the liver without the administration of glucose because of the progressing decrease of sugar concentration. However, there are so many factors that alter the rate at which the glucose content of the blood decreases after removal of the liver that the foregoing figure is meaningless unless carefully standardized conditions are maintained.

We soon noted that certain complications at the time of operation greatly increased the rate at which the blood sugar decreased. The more important of these complications were asphyxia, hemorrhage and venous stasis of some portion of the gastro-intestinal tract. In a few of our operations the diaphragm had been injured, causing pneumothorax with resulting asphyxia. In these instances the blood sugar decreased rapidly. Likewise the loss of an amount of blood at operation which ordinarily would not be considered as serious will cause the dehepatized animal to require much more than 0.25 gm. of glucose per kilogram per hour to maintain its blood sugar above the hypoglycemic level. In some instances the development of a collateral circulation necessitated partial occlusion of the venous return of a loop of intestine, usually the duodenum, at

the time of removal of the liver. The sugar disappeared from the blood at a surprisingly rapid rate in those animals in which this complication occurred. It was also observed that certain environmental factors affected the rate of development of hypoglycemia. The decrease of blood sugar was usually more rapid in a very active animal than in a quiet one. Exposure of the animal to cold or excessive heat increased the rate at which the blood sugar decreased (21). More glucose appeared to be required by those animals that became anuric shortly after operation than by the ones in which urine secretion was maintained. Bergman and Drury (22) noted this latter occurrence in eviscerated rabbits and pointed out its significance in studies on carbohydrate utilization in eviscerated preparations.

It has been our impression that the diet previous to removal of the liver influenced the rate at which glucose left the blood stream during the first few hours after operation (23). A previous carbohydrate diet appeared to hasten the disappearance of the sugar while a fast of a few days decreased the rate at which the sugar was lost from the blood and a diet of fat had an effect not unlike that of fasting. It has been impossible to date to quantitate our observations and after the first few injections of glucose the apparent difference disappeared. This problem deserves further study because of its importance and because of contradictory evidence in regard to it. Drury (24) noted that more sugar was needed in eviscerated rabbits that had been fed up to the time of operation than in those that had been fasted for three or more days previous to operation but the requirements tended to become the same after twenty-four hours and the actual survival time was not related to the fast. Soskin and Mirsky (25) found that the rate of disappearance of the blood sugar in eviscerated dogs was just as rapid in animals that had been fasted for periods of eighteen to thirty-eight days as in the control animals that had been fasted for two days. Roberts, Samuels and Reinecke (26) found that rats that had been maintained on a fat diet lived longer after evisceration than rats fed the standard diet.

The problem of whether or not the well-known alterations of metabolism induced by fasting and different diets that occur in the intact animal are continued in the extrahepatic tissue after removal of the liver is of such great importance in relation to metabolism of the major foodstuffs, action of endocrines and so forth that it deserves renewed investigation. The dehepatized animal is preferable to the eviscerated animal for such investigations because the former retains the insulin producing tissue. It should be noted that whatever effect fasting and the different diets may produce on metabolism is quickly dispelled by the injection of glucose.

We found that the standard amount of glucose, 0.25 gm. per kilogram per hour, was effective in preventing the development of symptoms of hypoglycemia only during the first few hours after removal of the liver. The dehepatized animal required more and more glucose as the length of life after operation increased (27). Whereas for the first twelve to eighteen hours 0.25 gm. per kilogram would suffice to prevent the development of symptoms, after this time 0.5 gm. of glucose was usually required and thirty hours after removal of the liver

even 1 gm. of glucose per kilogram each hour might not prevent the excitatory symptoms of hypoglycemia. The amount of glucose required at any one time appeared to depend to a considerable extent on the amount that had been previously administered, but was never less than the latter. The progressive increase of the amount of glucose required was dependent in part, at least, upon the development of the symptoms of hypoglycemia at progressively increasing blood sugar levels. The amount of sugar excreted in the urine might be considerable shortly after operation but this fact did not alter the aforementioned results and the dehepatized animal secretes very little urine thirty hours after operation.

The observation of the progressive increase of the amount of glucose required to maintain the dehepatized animal led to a study of the glucose tolerance after removal of the liver (28). It was found that if the test was made as soon as the animal had recovered from anesthesia and operation and the amount of glucose was 0.25 or 0.5 gm. for each kilogram of body weight, the resulting curves differed only in minor respects from the curves similarly obtained on the same animals before operation or on normal animals. These differences were (1) that the maximal increase of blood sugar might be greater and (2) that the rate of decrease at the normal blood sugar level was usually slower in the dehepatized animals than in intact animals. Also in dehepatized animals the blood sugar continued to decrease without recovery. As the tests were repeated successively, the sugar appeared to leave the blood faster in both the normal and liverless animals but the values at which spontaneous recovery of blood glucose began became less in the normal animal and the values at which it was necessary to give another injection of glucose to prevent hypoglycemic symptoms became greater in the dehepatized animal.

Pollack and his associates (29) carried out glucose tolerance tests, injecting the glucose at a constant rate into both normal and dehepatized animals and in some instances into the same animal before and after removal of the liver. Some control experiments were done on recently etherized animals. The amount of glucose injected was 2 gm. per kilogram per hour. In the control animals the levels of blood sugar averaged around 200 mg. in each 100 c.c. The excretion of sugar in the urine varied from traces during the first hour to a maximal amount of 0.15 gm. per kilogram per hour in subsequent periods. In the case of the dehepatized animals there was marked diminution of tolerance. Levels of blood sugar rose rapidly to 400 to 500 mg. per 100 c.c., with a secondary rise to more than 800 mg. per 100 c.c. when the kidneys failed to maintain uniform excretion. The urine contained from a minimal amount of 0.8 gm. of glucose per kilogram per hour to as high as 1.6 gm. per kilogram per hour.

Soskin and his associates (20) performed glucose tolerance tests on dehepatized dogs which were receiving a constant injection of glucose sufficient to maintain the blood sugar level at a constant height. They found that the amount of glucose usually required was 0.25 gm. per kilogram of body weight per hour. The blood sugar curves in the dehepatized animals had higher maximal values and the return to normal was much slower than occurred in normal animals. Soskin

and his associates attributed this result to a prompt diminution of the amount of sugar which the liver of the normal animal had been supplying to the blood from its own resources and concluded that the normal liver is a major factor in determining the normal dextrose tolerance test.

The combined results of our different investigations showed that while the dehepatized animal required a certain minimal amount of glucose in order to live and might evidence an increase of utilization for a short period after glucose was first administered, its tolerance for glucose was decreased as measured by the amount of glucose retained in the blood and excreted in the urine when the amount of glucose injected was greatly in excess of the minimal requirements. Furthermore, the level of blood sugar at which symptoms of hypoglycemia developed was increased in relation to time and the amount of glucose administered.

It was found that when the dehepatized animal had reached the stage at which relatively large amounts of glucose were required to prevent the development of hypoglycemia and the level of blood sugar at which these symptoms developed was no longer hypoglycemic, characteristic symptoms appeared and another condition developed (21, 30). The second group of symptoms consisted of the following, which are enumerated in the order in which they appeared: restlessness, ataxia, loss of sight and hearing, and finally coma in which death occurred. The appearance of the condition could be readily diagnosed by the fact that an animal which had been quiet for many hours suddenly would begin to walk around the room exploring everything within reach. At first its movements would be normal but in a very short time it would stagger as though drunk. It then began to bump into objects and on examination would be found to be unable to see or to hear. If it were in a cage it would lean or push its head against the cage wall. Coma would then supervene and after a variable period, some times several hours, death would quietly occur. Drury (31) has given an excellent description of this condition as it occurs in dehepatized rabbits.

The cause for the second group of symptoms and death of the dehepatized animal remains as one of the unsolved problems of the liverless animal. We have made numerous attempts to find some constituent in the blood that might have caused these symptoms and have injected unsuccessfully a large number of substances as therapeutic agents. Nothing so far has been found which appears to bear any relation to the development of the condition except the amount of glucose injected. The condition appears earlier in those animals in which the amount of glucose injected is greatly in excess of the minimal amount required. As previously mentioned, the dehepatized animal progressively requires increasing amounts of glucose to prevent the symptoms of hypoglycemia and the symptoms develop at gradually higher blood sugar levels. Suddenly the sugar tolerance appears to break and it seems to be at this stage that the second group of symptoms develops. These changes occurring in the blood sugar level of the dehepatized animal are not unlike those observed by Butsch (32) in normal dogs. He determined the glucose tolerance and glycogen storage capacity of normal dogs by the continuous injection of large amounts of glucose. He found that a rather sudden break in tolerance would occur and the blood

sugar would increase greatly. This sudden break in tolerance appeared to occur at the time the liver and muscles could no longer store the glucose.

Drury (24) noted the development of the second group of symptoms in dehepatized but not in eviscerated rabbits. Svedberg, Maddock and Drury (33) made the same observation. Since the eviscerated rabbits lived longer than those that were dehepatized Drury (24) concluded that the condition was owing to a toxin originating in the gastro-intestinal tract which was not destroyed in the absence of the liver.

Since the evidence indicated that the extrahepatic glycogen did not contribute much if any glucose to the blood of the dehepatized animal, it became important to attempt to determine if the extrahepatic tissue could make glucose from other substances. With the exception of the data previously given on fructose, we have not found any extrahepatic source of blood sugar. However, the minimal amount of glucose required by the dehepatized animal is relatively so large and so many factors affect the rate at which glucose leaves the blood after removal of the liver, that small amounts of glucose might be supplied from extrahepatic tissue without their being detected in the dehepatized animal.

Himsworth (34) has described small waves of variation of the blood sugar content of rabbits in which he had occluded the vascular supply of the liver by means of a special technic admirably suited for his purpose. He first attributed the waves in the blood sugar curves as indicating a source of extrahepatic glucose and later with Scott (35) explained them as partially due to increased utilization of glucose caused by a reflex secretion of epinephrine. At any event, regardless of the cause of the slight irregularities in the blood sugar curves, hypoglycemia always developed in Himsworth's animals after occlusion of the vascular connections of the liver.

Reinecke (17) has done some suggestive work on this question. He studied the kidney of the eviscerated rat as a source of blood glucose. He concluded that in the presence of the kidneys the concentration of sugar in the blood of the eviscerated rat at first falls but then remains at a nearly constant value for a period of many hours, a result which is in contrast to the precipitous decrease of blood sugar in the nephrectomized eviscerated rat. He also concluded that a fermentable reducing substance is added to the blood as it passes through the kidney.

Much more work on the problem is necessary before it can be accepted that there are extrahepatic sources of glucose for maintenance of the blood sugar. The use of glucose by the living organism is so universal that there would appear to be no reason to doubt that mechanisms for contributing glucose to the blood are present in many different kinds of tissues but such anhepatic mechanisms have so far defied detection in the dehepatized dog.

Since the normal concentration of the blood sugar was not maintained in the liverless animal, it was important to determine whether the usual methods for causing physiologic alterations of blood sugar values would be operative in the absence of the organ. Briefly it was found that removal of the liver (1) caused hypoglycemia in an animal previously made hyperglycemic by removal

of the pancreas, (2) did not prevent the hypoglycemic action of insulin and (3) prevented the hyperglycemia which in the presence of the liver occurs after anesthesia and operation, asphyxia and the administration of epinephrine.

Magath and I (30, 36) found that removal of the pancreas did not fundamentally alter the effect of removal of the liver on the blood sugar. When the two organs were removed at the same time, the effect was the same as though only the liver had been removed. When the liver was removed at a sufficient length of time after removal of the pancreas to permit hyperglycemia to occur, the blood sugar decreased quickly and the symptoms of hypoglycemia developed as after removal of the liver but at a higher blood sugar level. The injection of glucose restored the dehepatized, pancreatectomized hypoglycemic animal to normal but the effect of the glucose was very fleeting. These experiments proved that the depancreatized animal utilized glucose.

Houssay (37) and his students found that removal of the liver prevents the increase of blood sugar in hypophysectomized, pancreatectomized toads by anterior pituitary lobe extract and causes the blood sugar to decrease in the dog with diabetes of pituitary origin with glycemia due to injection of the extract. We found that the hypoglycemic action of insulin persisted in the dehepatized animal (38, 39).

The results of our investigations on the effect of removal of the liver on the transitory hyperglycemia produced by various methods such as anesthesia and operation, asphyxia and administration of epinephrine were definite. While such procedures produce hyperglycemia in a normal animal, they were found to be ineffectual in the dehepatized one (27). This result has been amply confirmed by Soskin (40). Evidently, if extrahepatic sources of glucose are present in the body, they either do not respond to the usual methods or have an insufficient capacity to cause hyperglycemia.

The fate of lactic acid in the dehepatized animal has not been fully determined. Lactic acid and its salts do not substitute for glucose in restoration from hypoglycemia (30). Lactic acid increases in the blood of the liverless animal but large amounts of injected lactate will also disappear from the blood after removal of the liver. We have some suggestive data indicating that glycogen in the muscle of the dehepatized animal increases after the injection of lactates and Petersen (41) reported that glycogen is made in the mammary gland from lactic acid.

In an attempt to determine the fate of the glucose that disappeared in the liverless animal and to learn whether or not loss of all the hepatic tissue causes significant alterations in metabolism, Boothby and I (42) studied the energy metabolism of animals before and after removal of the liver. We found that when extraneous factors were eliminated, the metabolism of the dehepatized animal differed in only a few respects from that of a normal animal or of the same animal before removal of the liver. The total amount of heat produced was not directly affected by the loss of the liver. The most significant findings were (1) that the respiratory quotient increased immediately after removal of the liver and (2) that glucose had a greater specific dynamic action in the dehepatized

animal than in a normal one. Markowitz (43) obtained similar results. Since the specific dynamic action of glucose was increased in the dehepatized animal, it was pertinent to inquire whether or not removal of the liver produced an alteration of the specific dynamic action of amino acids, especially as the latter appears to be so much more significant than that of glucose in the normal organism. Wilhelmj, Bollman and I (44) found that the specific dynamic action of the amino acids, alanine and glycocoll, was absent in the dehepatized animal.

There is considerable controversy in regard to the value and interpretation of the data obtained by investigations dependent upon use of the respiratory quotient. The subject is too great to warrant discussion here but since my colleagues and I have devoted much time to our studies on the gaseous metabolism of the normal and dehepatized animal I believe our present opinion on the question should be stated. Since several metabolic activities may be taking place in the organism at the same time which may affect the respiratory quotient differently, the objection to acceptance of the quotient as proof of the type of food being used and the manner of its utilization would appear to be valid. On the other hand, I am satisfied that the method of studying the gaseous metabolism of the dehepatized animal has been a tool whereby we have learned some things that could not have been learned by any other method.

In passing, it should be noted that while the value of the respiratory quotient of the intact animal has been seriously questioned, the use of the quotient of tissue slices has received only mild objections. I am of the opinion that the objection stated previously is as fully applicable to the respiratory quotient obtained from slices of hepatic tissue as to that obtained from the dehepatized animal. The functions of the hepatic cell are numerous and some of the physiologic processes that occur in this cell are just the ones which may cause the greatest alterations of the respiratory quotient. It is known that several of these different processes are taking place in the hepatic cell at the same time. Furthermore, cytologic studies have demonstrated that not only are not all the hepatic lobules equally active at the same time but also that there are zonal activities of different kinds within the lobule. In addition there are three other cell types besides the hepatic cell in the tissue of the liver and while the total amount of the former is small compared with that of the latter, the possible effect that their metabolism may have upon the respiratory quotient cannot be ignored. It would appear very unlikely that the respiratory quotient of a slice of hepatic tissue is any less the result of the sum total of the numerous physiologic processes occurring in liver which give origin to wide variations in gaseous exchange than the processes which affect the respiratory quotient of the dehepatized animal.

One of the first functions in relation to metabolism allotted to the liver was the formation of urea. The results of some of the early investigators appeared to indicate that the liver specifically made urea but there were so many experiments in which the results were negative or contradictory that the whole question remained in doubt. We were unable to demonstrate the formation of any measurable amounts of urea in the dehepatized animal (45). The disposition

of the urea content of the dehepatized animal appeared to be determined by the amount of secretions, such as urine, saliva, gastric juice and so forth, in which urea may be excreted. If a satisfactory secretion of urine could be maintained, the liverless animal would become almost urea free and this decrease of the urea content of the blood and tissues could be accounted for by the amount of urea and ammonia excreted in the urine. As nearly as could be determined, the making of urea ceased immediately after removal of the liver. No contrary evidence to this deduction has been produced. The only other site in the body in which it has been proved that urea is formed is the actively secreting mammary gland (8). The amount of urea made in this fashion would appear to be too small to be detected in the intact animal.

If urea is not made in the dehepatized animal, what becomes of the nitrogenous products which in the normal animal give origin to the nitrogen that is excreted as urea? This question was readily answered in regard to the main source of such nitrogen but there remains a question concerning certain minimal amounts. It was found that the amino acids increased in the blood, urine and muscles after removal of the liver. The amount of amino acids recovered from these sources was approximately equal to the estimated amount of urea that would have been found if the animal had been normal. Furthermore, there was no appreciable increase of other nitrogenous products, so that the nitrogen which normally goes into the formation of urea could not be accounted for by the accumulation of such undetermined substances. The administration of amino acids to the dehepatized animal increased the amino-acid content of the blood, urine and tissues and the amount of amino acids administered could be found in these sites. The administration of the amino acids did not alter the urea content of the blood, urine or tissues. This result is in marked contrast to that obtained in normal dogs in which a large amount of the amino acids is rapidly converted to urea. Nor did the administered amino acids, in the absence of the liver, appreciably alter the ammonia content of the blood, urine or tissues. There was also no evidence of the formation of glucose from amino acid after removal of the liver. The decrease of blood sugar continued unabated and the symptoms of hypoglycemia were not averted (46).

While alterations of the ammonia content of the blood and urine occurred in the liverless animal, these changes were not of a sufficient magnitude to account for the nitrogen which did not appear as urea if deamination were proceeding at the normal rate. The ammonia in the blood and tissues was usually found to be increased after removal of the liver. A considerable portion of this ammonia apparently came from the gastro-intestinal tract and was independent of the ammonia found in the urine. The ammonia in the urine of the liverless animal was found to be dependent upon the acid-base equilibrium of the body to about the same extent as occurs in normal animals. The ammonia in the urine progressively decreased with the decrease of urea although at the same time the urine contained large amounts of nitrogenous substances as amino acids and uric acid (47).

Since the results of all our experiments indicated the same thing, a failure of

deamination to occur after removal of the liver, we felt justified in concluding that in the dog the deamination of amino acids is entirely dependent upon the presence of the liver. This conclusion has been questioned in some slight respects. Probably the most conclusive evidence that some deamination occurs outside the liver has been supplied by investigations which indicated that some amino acids were deaminized by slices of kidney. An appraisal of these data indicates that if the amount of deamination occurring in the kidneys were relatively no greater than the amount found in the slices of kidney, it would be very difficult to detect the process in the intact organism by means of available methods. Removal of both kidneys does not decrease the rate of deamination in an animal whose liver is intact as compared with a normal animal. Folin (48) stated that deamination is such an important process that in all probability it would not be limited to any one tissue or organ but would be a function of all tissues. We would not argue against the logic of his statement but the fact still remains that with available methods it has been impossible to detect any deamination as occurring in the dehepatized animal.

The first specimen of urine secreted by the dehepatized animal contains, upon cooling, a precipitate, which increases progressively in succeeding specimens until about half the volume of urine may be composed of a white, flocculent precipitate. The urine from a liverless dog is so different in appearance from that of a normal dog that it immediately attracts attention. A hasty glance at this precipitate under the microscope indicated that it was composed of pigmented crystals of urates. Since purine metabolism in man differs in some respects from that in many other species of animals, including most breeds of dogs, I shall only summarize the results of our investigation on this subject. Normally the uric acid found in the dog is changed into allantoin and excreted in the urine in this form. In the dehepatized animal this transformation of uric acid to allantoin does not occur and the uric acid found is excreted in the urine or accumulates in the blood and tissues (49, 50). Maddock and Svedberg (51) found that uric acid increases in the blood and urine of the dehepatized monkey.

Numerous studies by different methods have indicated that the liver is primarily involved in the formation of the plasma proteins. The results of the investigations of Whipple (52) and his associates suggest that the liver is of primary importance in body protein metabolism and prove that hepatic activity is involved in plasma protein production. Berryman, Bollman and I (53) found that in the dehepatized animal there is a definite decrease of the total protein. The decrease of the various fractions might have been owing to dilution except for that which occurred in the euglobulin and especially the fibrinogen. When plasmapheresis involving a third or a half of the total blood volume was carried out in the liverless animal, there was no evidence of regeneration of the plasma proteins although the dehepatized animals lived for a length of time during which a measurable amount of regeneration occurs in normal animals which have been maintained on the same diet as those from which the liver was removed.

Investigation of the dehepatized animal has so far proved to be of little value in helping to solve the mystery of fat metabolism but it has not been much more

barren in this respect than many other methods. In a difficult but well-conducted investigation Drury and McMaster (54) found that rabbits which previous to operation had been fed on fat retained the low respiratory quotient of 0.7 after removal of the liver, thus indicating that the dehepatized animal utilizes fat. The results of the previously mentioned work of Roberts, Samuels and Reinecke (26) would also indicate that the extrahepatic tissues burn fat after removal of the liver. Chaikoff and Soskin (55) found that the ketone bodies which accumulated in the depancreatized animal disappeared very rapidly after evisceration. Nevertheless it should be emphasized that hypoglycemia always occurs in the fat-fed, dehepatized animal, indicating that glucose is essential.

The blood pressure of the dehepatized animal is within normal values immediately after an uncomplicated operation and will remain thus for many hours if a sufficient amount of glucose is administered to prevent hypoglycemia. Blood pressure decreases with the onset of hypoglycemia and while glucose has a beneficial action, complete restoration to normal does not occur. The alterations of respiration and temperature that occur after removal of the liver and that are not associated with hypoglycemia, appear to be for the most part associated with anesthesia, operation and environmental factors rather than with loss of the liver. Respiration always ceases before the heart or complete failure of the circulation in death of the liverless animal.

The dehepatized animal usually has tachycardia. The cause for the increase of heart rate after removal of the liver remains an unsolved problem. The increase of heart rate is of a magnitude of 40 to more than 100 per cent. There are many possible causes for this result but it is apparently not due to some of the more obvious ones. After comparing the alterations of heart rate that occur after various operative procedures we have concluded that the tachycardia after removal of the liver is more consistent, greater and longer sustained than after any other operation on which we have data. It is not due to loss of blood at operation. The increase of heart rate occurs immediately after removal of the liver and usually persists throughout the life of the animal, although a slow vagal type of beat may occur for short periods during hypoglycemic convulsion. The tachycardia cannot be correlated with the decrease of blood sugar. It is present at a time when the blood pressure is within normal limits. It does not appear to be owing to the secretion of epinephrine or stimulation of the sympathetic nervous system, although these two factors have not been entirely eliminated. In a few instances the rate of a perfused rabbit heart increased when blood from a dehepatized animal was added to the perfusate but the results of this type of experiment have not been consistent. The problem requires further investigation.

The importance of the liver in the formation of lymph in various physiologic activities and following the injection of certain substances is real but has probably been overemphasized in relation to the amount of lymph produced by the whole body. C. Markowitz and I (56) found that the flow of lymph from the thoracic duct was not decreased by total removal of the liver and that the intravenous injection of such substances as peptone and glucose produced an increase

of the flow of lymph that did not differ greatly from that occurring in a normal animal.

It has been repeatedly demonstrated since the original work of Fiske (57) that there is a specific relationship between carbohydrates and phosphates. Hyperglycemia in the normal organism is associated with a decrease of concentration of phosphate in the serum followed by a gradual return to the normal value. Pollack and his associates (58) studied the effect of the administration of glucose on the serum phosphates in normal and dehepatized animals. They found that the continuous intravenous injection of glucose in amounts that caused hyperglycemia was associated with a rapid decrease of serum phosphate in both normal and liverless animals and in both groups, even with the continued injection of glucose, there was a gradual return of the phosphate concentration to the preinjection values. However, both the decrease and the restoration of the serum phosphate were more rapid in the dehepatized animals than in normal animals. Best and his associates (59) studied the responses of the inorganic phosphate of the blood to insulin in the functionally dehepatized animal and concluded that the alterations of phosphate were not wholly dependent on the liver.

The liverless dog becomes jaundiced. There is no longer any doubt that the pigment which accumulates in the blood and tissues after removal of the liver is bilirubin. It has not been proved that the hepatic cell does not form bilirubin but the fact that the rate of development of the bilirubinemia of the dehepatized animal is so nearly the same as that of a normal animal following removal of the gallbladder and obstruction of the biliary outflow would appear to prove that a large percentage of the bilirubin excreted by the liver can be made outside the organ. The evidence indicates that the bile pigments are formed in the reticulo-endothelial cells throughout the body, including the stellate cells in the liver, and that the hepatic cells only excrete the pigment (60, 61). This fact would suggest that any hypothesis concerning the different types of jaundice should include a consideration of the processes of passage of the pigment through the cells lining the hepatic sinusoids and the penetration of the hepatic cells. Variations of the threshold of these two groups of cells for bilirubin may be a significant factor.

Lack of a wholly satisfactory method for quantitating the bile salts in the blood and urine makes it necessary to use discretion in regard to statements concerning these substances in the liverless animal. However, using the methods available, it would appear that bile salts are no longer made after removal of the liver and that injected bile salts disappear much more rapidly from the blood of an animal in which the liver is present than from the blood of one in which the organ is absent. We have interpreted these findings to mean that the liver makes and also destroys bile salts (62).

One of the most common but at the same time most indefinite functions ascribed to the liver is that of detoxication. A detoxicating hepatic activity is difficult to prove in respect to specific substances but observations on the liverless animal indicate that the organ may be a protector of the body from noxious

agents. Specifically it can be demonstrated that some alkaloids, such as strychnine (63) and nicotine (64), are destroyed in relatively small amounts in the dehepatized animal. We have observed that the administration of many substances in amounts that are innocuous to a normal animal may produce serious consequences when given to the dehepatized one. The liverless animal will tolerate a physiologic dose of very few drugs and many substances in common use as local anesthetic agents, hypnotics and so forth must be given in half or less of the usual amount to a dehepatized animal if reactions are to be avoided. Even the intravenous injection of normal constituents of the blood, such as amino acids, ammonia, lactic acid and so forth, in amounts which are harmless to the normal animal produces severe reactions in the absence of the liver. The mechanism whereby the liver protects the body from injurious substances is not known. The liver may deal with some toxic substances by conjugation but certainly not with all such substances. The rate of conjugation of phenol injected into the dehepatized animal is little altered from that of a normal animal but the tolerance to phenol is greatly decreased by removal of the liver. It would appear that the liver protects the body (1) by absorbing certain substances like a sponge, such as the accumulation of amino acids in hepatic tissue, and (2) by specific chemical alteration of other substances, such as the conversion of ammonia into urea.

Evidence that the liver is an important factor in relation to the process of coagulation of the blood has been accumulating for many years. Investigations have been made on animals in which the liver was injured, following occlusion of the blood vessels to the organ and after removal of the liver. It would appear that the liver is the site of formation of both the fibrinogen (53, 54) and the prothrombin. However, alterations of the coagulation of the blood of a dehepatized animal are often not very great, a fact which would appear to indicate that a certain reserve amount of the constituents for forming the clot is present in the liverless animal. Fairly frequently neither the time of clotting nor the character of the clot changes significantly throughout the length of life of the dehepatized animal. The clotting time often increases and more frequently the character of the clot is altered in respect to a decrease of contractility and increase of friability. It is not rare for the dehepatized animal to bleed owing to a failure to form a solid clot.

The mechanism whereby hypoglycemia causes death remains as an important and only partially solved problem. We soon learned from our observations on the dehepatized animal dying in hypoglycemia that the respiration always stopped before the heart. It has frequently been possible to restore the animal in hypoglycemia after respiration had ceased by applying artificial respiration while injecting glucose. All the major symptoms that appear as the blood sugar decreases can be referred to the central nervous system. This fact would appear to prove that the central nervous system requires the presence of glucose in order to function. It is not so evident from observations on the liverless animal whether other tissues also require glucose to maintain life.

We interrupted our studies on hypoglycemia when the hypoglycemic action of insulin was discovered because it was evidently easier to inject insulin than to remove the liver. The results of studies on hypoglycemia produced by removal of the liver and by the injection of insulin have been mutually corroborative. Most of the facts that are known about the effects of a low blood sugar on the various physiologic activities of the body have been learned through the use of insulin. However, in such experiments the presence of the liver has remained as a possible source of error in interpretation of the results of studies on hypoglycemia produced by insulin.

Recently we have renewed our investigation on the mechanism of death in hypoglycemia. The objective of the research was to attempt to maintain artificially those functions of the body which appeared to cause death in the dehepatized hypoglycemic animal and thus to learn what physiologic activities would persist in the absence of glucose. The investigation is in a preliminary stage and some of the difficulties encountered have not been overcome. Briefly, the simple method used to date and the results obtained are as follows: The liver is removed in the usual manner. When the animal becomes hypoglycemic, the trachea is intubated and artificial respiration is started just as the animal's respiratory movements cease. It is thus easy to substitute for the lost respiratory function but so far it has not been possible to prevent or restore the progressive decrease of blood pressure which occurs as the hypoglycemia develops and which without the administration of glucose will fall to shock levels.

No evidence of activity of the central nervous system has been detected in these almost glucose free animals. Yet in one animal, three hours after respiratory movements had ceased, the injection of glucose restored respiration and partially restored blood pressure, many of the reflexes returned and uncoordinated movements occurred. There was no evidence of cerebral function. It should also be noted that during the three hours the concentration of blood sugar was very low but, in the absence of artificial heat, the rectal temperature decreased only a few degrees below normal. This would suggest that substances other than glucose were being burned. While so far nothing new has been learned from the results of these experiments, they have served to emphasize the fact that glucose is essential for maintaining the physiologic activity of the central nervous system and hence the life of the whole organism.

In this lecture I have attempted to review the more important facts that have been learned from studies on the dehepatized animal. By inference I have attempted to show that when the liver is removed the continuity of many of the physiologic processes that occur in the organism is broken and that numerous hepatic and extrahepatic activities are mutually interdependent. If I have accomplished those two objectives it should be evident that studies on the liverless animal will give only an incomplete picture of the sum total of hepatic functions. It should be equally evident that removal of the liver has afforded a means for discovering some facts concerning wholly extrahepatic physiologic processes. Of the latter I wish to emphasize only one: that glucose is essential for life in the higher organisms and appears to be as irreplaceable as oxygen.

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THE EFFECT OF CERTAIN QUINONES, ALDEHYDES AND KETONES ON THE BLOOD PRESSURE OF HYPERTENSIVE MAMMALS¹

B. S. OPPENHEIMER, M.D., SAUL SOLOWAY,² Ph.D.,
AND B. E. LOWENSTEIN,² M.D.

Previous experimental work has demonstrated that it is possible to cause a drop in the blood pressure of hypertensive rats by oral or parenteral administration of certain of the quinones (1, 6, 7, 8). These results have since been confirmed by two other groups working independently (2, 3), so that now we have evidence from three separate laboratories, using two different methods for measuring the blood pressure of the rat, that these quinones are effective antipressor agents in the rat. Therefore, despite some uncertainty concerning the theoretical considerations involved, it seemed worth while to extend these observations to the higher mammals, and to increase the number of compounds tested.

Methods. Three different species of mammals were rendered hypertensive and were used for the experiments reported here: Rats were made hypertensive by the application of a cellophane wrapping of one or both kidneys. Their blood pressures were measured by the method of Williams, Harrison and Grollman (4). Dogs were made hypertensive by the application of either a cellophane wrapping or a Goldblatt clamp to one or both kidneys. Their blood pressures were measured either by direct cannulation of the femoral artery, or else indirectly by use of an ordinary sphygmomanometer (with a dog cuff) and stethoscope. Monkeys were made hypertensive with similar methods. Blood pressures in monkeys were measured in the same way as in dogs. No drop in blood pressure was considered significant unless it measured 30 mm. Hg. or more. The toxicity of some of the substances used was also tested on normal guinea pigs, rabbits and cats.

Results. In a previous communication (1) it was shown that the blood pressure of hypertensive rats is lowered significantly by several of the paraquinones; orthoquinones with one exception were without effect in our experience. Of these active quinones, those that were considered least toxic and most effective were tested on dogs. These quinones were thymoquinone, sodium rhodizonate, and 1,4-naphthoquinone. There was difficulty with the solubility of many of the quinones, so we turned to some of the sulfonated derivatives.

From Table 1 it may be seen that these three quinones proved extremely

¹ From the Laboratories of The Mount Sinai Hospital, New York City.

² Dr. Soloway of the Grosvenor Laboratories, N. Y., and Dr. Lowenstein have acted in an advisory capacity in this research, but neither has been on the staff of the Mt. Sinai Hospital during this work. Captain Ben Friedman, who directed our previous work on the quinones, has been in the Army since September 1942 and is still overseas.

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TABLE 1
Showing the effects of quinones, aldehydes and ketones on hypertensive mammals: dogs, rats and 1 monkey

SUBSTANCE TESTED	DAILY DOSE	METHOD OF ADMINISTRATION	MEDIUM	HYPER-TENSIVE ANIMAL	NUMBER OF ANIMALS	EFFECT ON BLOOD PRESSURE*	EFFECT ON THE BLOOD PRESSURE OF THE NORMAL ANIMAL	TOXICITY	REMARKS
Quinones	mg.								
Sodium rhodizonate	100-300	Intramuscular	Saline	Dog	2	+	0	Local edema; fever	
Sodium rhodizonate	250-350	Intravenous	Saline	Dog	3	0			
Sodium rhodizonate	300-400	Intravenous	Saline	Dog	{ 2 1	+	0		
Sodium rhodizonate	150-225	Intravenous	Saline	Monkey	1	+			
Sodium rhodizonate	100	Oral	In food	Rat	6	±			
Na-thymoquinone sulfonate	50-100	Intramuscular	Saline	Dog	2	0	0	3 deaths Local edema at 100 mg. in hypertensive dog	Effect short-lived in acute experiment Effect short-lived; repeated four times
Na-thymoquinone sulfonate	100	Intravenous	Saline	Dog	2	0	0		
Na-thymoquinone sulfonate	5-10	Subcutaneous	Saline	Rat	6	+			
1,4-naphthoquinone	60-300	Subcutaneous	Olive and sesame oil	Dog	4	+		1 death; all had local necroses	
Na-β naphthoquinone 4-sulfonate...	10-20	Subcutaneous	Saline	Rat	6	+	0	1 death; all had local necroses	
Na-β naphthoquinone 4-sulfonate...	400	Subcutaneous	Saline	Dog	3	0		1 death; all had local necroses	
Na-β naphthoquinone 4-sulfonate...	100-200	Intramuscular	Saline	Dog	3	0		Brawny edema in all dogs	
Na-β naphthoquinone 4-sulfonate...	50-75	Intravenous	Saline	Dog	3	±		2 deaths	
Nn-β naphthoquinone 4-sulfonate...	200-800	Oral	Saline	Dog	3	0			
2,6-dichloroquinone	5-20	Subcutaneous	Olive oil	Rat	6	+	0		Less active than thymoquinone (1 dose-30 mg.)
2-methyl-α-naphthoquinone (menadiolone)	10-15	Subcutaneous	Olive oil	Rat	6	+			
2,3-dimethyl-α-naphthoquinone...	5-20	Subcutaneous	Olive oil	Rat	5	0			
5,8-dihydroxy-α-naphthoquinone (juglone)	2	Subcutaneous	Saline and sesame oil	Rat	6	0			
Aldehydes									
Reductone	10-30	Subcutaneous	Saline	Rat	6	0		2 deaths; all had local ulcerations	
Glyoxal	5-15	Subcutaneous	Water	Rat	11	+	+		

Glyoxal	20	Oral	Water	Rat	5	±		1 death; all had local ulcerations
Succinic dialdehyde	5-10	Subcutaneous	Water	Rat	5	+		Moderate local edema
Adipic dialdehyde	5-30	Subcutaneous	Water	Rat	5	0		Moderate local edema
Methyl glyoxal	5-15	Subcutaneous	Water	Rat	5	±		Moderate local edema
Ketones								
Cyclopentanone	5-20	Subcutaneous	Water	Rat	5	0		
Cyclohexanone	5-15	Subcutaneous	Water	Rat	5	0		
1,2-cyclohexandione	10-30	Subcutaneous	Saline	Rat	6	0		2 deaths
1,4-cyclohexandione	10-30	Subcutaneous	Saline	Rat	6	mild	+	0
Diacetyl	4-15	Subcutaneous	Water	Rat	5	0		0
Acetyl acetone	5-20	Subcutaneous	Water	Rat	5	0		1 death
Acetonyl acetone	5-20	Subcutaneous	Water	Rat	5	0		1 death
Camphloquinone	5-20	Subcutaneous	Triacetin	Rat	6	0		1 death
Sodium oxalacetate	10-40	Subcutaneous	Saline	Rat	5	0		
Miscellaneous								
Decoumarin	5-10	Subcutaneous	Saline and propylene glycol	Rat	6	0		1 death
Hydroquinone and hydroquinone sulfonate	10	Subcutaneous	Saline	Rat	6	0		1 death
Testosterone propionate	5-15	Subcutaneous	Peanut oil	Rat	5	0		
Parabanic acid	5-30	Subcutaneous	Saline	Rat	5	0		

* + = antipressor effect.

toxic to dogs when injected subcutaneously or intramuscularly, causing extensive induration, edema, and even local necroses at the site of injection. For these reasons, the injections were discontinued, as no very significant effect on blood pressure was observed. Oral administration was ineffective even when very large doses were used.

Intravenous injection of the sodium rhodizonate caused a drop in the blood pressure of the hypertensive dog and the hypertensive monkey, but these drops were quite temporary. Repeated intravenous administration of sodium- β -naphthoquinone-4-sulfonate caused a moderate fall in the blood pressure of three hypertensive dogs, but two of these animals died during the period of administration.

In view of these results, it was considered that these three quinones were of no practical use in the treatment of hypertension in dogs. An attempt was made to lessen the toxic effects by adding alkyl side chains, but 2-methyl-naphthoquinone (menadione, pro-Vitamin K) was effective only in relatively large doses, and 2,3-dimethyl-naphthoquinone was entirely inactive in hypertensive rats.

In respect to Vitamin K preparations, we tested menadione (2-methyl-1,4-naphthoquinone) on six hypertensive rats in January 1943 and found it had an antipressor effect in doses of 10-15 mg. of the compound dissolved in olive oil, administered subcutaneously. A casual review of clinical observations on the possible antipressor effect of Vitamin K in the ordinary therapeutic doses in hypertensive human beings did not reveal any lowering of blood pressure: but this review was made only after the appearance of the paper by Schwarz and Ziegler (5).³

We decided to determine whether other dicarbonyl compounds possessed this antipressor action without producing the extreme toxic effects of the quinones. A large series of aliphatic dialdehydes and diketones and cycloketones was therefore tested for effectiveness in lowering the blood pressure of hypertensive rats. These results are summarized in Table 1. From this table, it may be seen that the diketones were, in general, inactive with the exception of 1,4-cyclohexandione which was mildly antipressor in six hypertensive rats; it had no influence on the blood pressure of four normal control rats. Some preliminary observations on the influence of 1,4-cyclohexandione in hypertensive dogs indicate a decided antipressor effect of this compound and lack of toxicity (local or general) in the dosage so far employed; the results of these experiments are not yet completed and therefore are not recorded in Table 1.

³ Recently and quite independently Schwarz and Ziegler (5) have published an interesting paper on the "Influence of Vitamin K Preparations on the Blood Pressure of Hypertensive Rats." They found that Vitamin K (menadione) was antipressor in nine experiments with a dosage of 5-10 mg. administered intramuscularly in rats rendered hypertensive by the Page technique of wrapping both kidneys in silk. Another rat did not respond to menadione. On the other hand, five hypertensive rats did not show antipressor effects during the period of daily injection of 10 mg. of Synkayvite, Roche (the water soluble hydroquinone compound, 2-methyl-1,4-naphthohydroquinone, diphosphoric acid ester tetrasodium salt). Schwarz and Ziegler are considering the trial of Vitamin K in human hypertension, and their results will be awaited with great interest.

The dialdehydes, although active, showed a marked local toxic effect and therefore were not available for general use. Lengthening the carbon chain was of some value in decreasing toxicity, but also resulted in an even more rapid decline in antipressor activity. It is remarkable that one of these dialdehydes (glyoxal) was sufficiently toxic to result in the lowering of the blood pressure of normal rats. For these reasons the active dialdehydes were not tested on hypertensive dogs. Oral administration of dialdehydes was unsatisfactory.

In Table 1 are also summarized the results of administration of a number of miscellaneous unsaturated oxygen-containing compounds, which were ineffective in lowering the blood pressure of hypertensive rats. These compounds were testosterone, parabanic acid, hydroquinone, and dicoumarin.

SUMMARY AND CONCLUSIONS

1. There are 5 quinones in these experiments which have more or less antipressor properties when tested on hypertensive mammals. These are

- (a) Sodium rhodizionate
- (b) Sodium thymoquinone sulfonate
- (c) Sodium β -naphthoquinone-4-sulfonate
- (d) 2,6-dichloroquinone
- (e) 2-methyl- α -naphthoquinone

The first three of these proved to be toxic when tested on hypertensive dogs.

2. Oral administration of the quinone, sodium β -naphthoquinone-4-sulfonate to 3 hypertensive dogs was ineffective.

3. A search among the dialdehydes and diketones for effective antipressors on hypertensive rats and dogs has yielded one promising lead in 1,4-cyclohexandione. In the doses employed so far 1,4-cyclohexandione has not produced toxic effects.

4. Further studies on the antipressor effects of 1,4-cyclohexandione on hypertensive dogs are now in progress.

The authors gratefully acknowledge the assistance of Prof. Homer B. Adkins who supplied us with 1,4-cyclohexandiol, to Prof. R. C. Elderfield who converted this into 1,4-cyclohexandione, to Prof. Louis F. Fieser and to the Wallerstein Laboratories for certain compounds.

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ESSAYS ON THE BIOLOGY OF DISEASE¹

ELI MOSCHCOWITZ, M.D.

CHAPTER 4

THE BIOLOGICAL EVOLUTION OF TOXIC HEPATITIS

Toxic hepatitis or infectious hepatitis is conventionally classified into two forms, "catarrhal icterus"² and "acute yellow atrophy" with the implication that they are two separate and distinct diseases, the main distinction being that in "catarrhal" icterus, the patient recovers while in acute yellow atrophy the patient dies. This distinction, however, is not valid because occasionally "catarrhal icterus" passes imperceptibly into "acute yellow atrophy" with fatal outcome and on the other hand, cases of "acute yellow atrophy" may recover. Such transitions lead one to suspect that the two diseases are identical, and this is confirmed by their morphologic identity. In the few autopsies that have been reported on patients who have died by accident with what appeared to be clinical "catarrhal icterus" and by biopsy, degeneration of the liver with focal areas of necrosis were found, precisely, similar to those witnessed in the early phases of acute yellow atrophy (Eppinger (1), Klemperer, Kilian and Heyd (2)). Indeed, these observers hold that "catarrhal icterus" is identical with acute yellow atrophy differing only in degree. Eppinger calls catarrhal icterus "acute yellow atrophy en miniature." Moreover the two diseases possess clinical similarities. For instance, in both there is a lowered cholesterol and cholesterol ester in the blood (Ottenberg and Spiegel (3)), and the tyrosinuria, which formerly was regarded as pathognomic for acute yellow atrophy is found by the more delicate methods devised by Lichtman and Sobotka (4) in many cases of "catarrhal icterus." The galactose test for liver function which indicates more or less quantitatively parenchymal damage is more frequently positive in catarrhal icterus and acute yellow atrophy than in any other hepatic disorders (Ottenberg and Spiegel (3)). Finally, the epidemiologic incidence between the two diseases is identical (Bergstrand (5)).

In the acute phases of toxic hepatitis, therefore, a wide variety of clinical manifestations are observable varying from a mild form with complete recovery to that conventionally described under the heading of "acute yellow atrophy" ending in death from cholemia or from the so-called hepato-renal syndrome.

¹ This is the fourth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the JOURNAL OF THE MOUNT SINAI HOSPITAL. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

² "Catarrhal" icterus is probably not a single disease, but a syndrome, the result of various morphologic backgrounds. We are not referring to cases due to a swelling of the papilla of Vater due to a gastroduodenitis or to a cholangitis.

Most cases of "catarrhal" icterus, therefore, are potentially acute yellow atrophies.

If the patient survives, regeneration arising from the intact areas of hepatic parenchyma ensues, which, depending upon the extent of destruction and of survival of the parenchyma, may vary from slight connective tissue replacement with slight or moderate compensatory hypertrophy of the remaining liver lobules to extensive band-like infiltration of connective tissue and the formation of compensatory adenomatous-like masses throughout the liver. These represent end results and have received different eponyms, e.g., "toxic cirrhosis" (Mallory (6)), "nodular sclerosis," "nodular hyperplasia" and "multiple adenomata of the liver." The clinical expression of toxic hepatitis does not always parallel the morphologic, as evident from the observation that not infrequently the patient dies early in the course of the disease, while at autopsy the subacute or chronic stage is found. First, this proves the malady is sometimes dormant long before the clinical manifestations appear. This was shown by English observers in World War I, when it was noted that in workers in trinitrotoluene, the disease manifested itself weeks and sometimes months after cessation of contact (Rolleston (7)); and second, the regenerative power of the liver is enormous and death usually comes only when there is not sufficient normal hepatic tissue to carry on adequate function.

It matters not what the cause of the toxic hepatitis may be; whether it is known, as for instance, phosphorus, chloroform, carbon tetrachloride, mushrooms, syphilis, salvarsan, etc. or unknown, with the lesions resembling those of acute yellow atrophy so closely as to be practically indistinguishable. Furthermore, the anatomic end-results are alike.

Whether a complete anatomical restoration to normal occurs in toxic hepatitis is doubtful; as in cases of acute glomerulonephritis, the earliest healed phase is unknown. That complete anatomic recovery does not in all likelihood occur is shown by Soffer and Paulson (8) who, using the bilirubin excretion test in eleven patients who had toxic hepatitis several years previously, found that in nine there was a retention of between 10 to 50 per cent at the end of four hours. Between this early phase, which gives little or no clinical manifestations and the terminal, designated by such terms as toxic cirrhosis, nodular sclerosis, nodular hyperplasia, etc. gradations in clinical severity accompanied by various degrees of morphologic changes occur depending in all probability, as previously noted, upon the extent of initial destruction and the capacity for regeneration. This intermediate phase is termed "subacute" or "red atrophy of the liver."

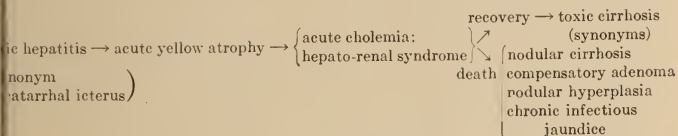
In the vast majority of instances, as far as morphology is concerned, the biological course is complete when toxic cirrhosis, nodular hyperplasia, etc. are produced.

The fate of the patient depends largely upon the extent of the damage and the degree of regeneration. If the expression of the disease has been mild, the patient may reveal nothing clinically but an enlarged and perhaps irregular liver and an enlarged spleen, and he eventually succumbs to a totally unrelated malady. If severe, he may die from progressive hepatic insufficiency with jaundice and

cholema or he may develop, as in other forms of cirrhosis, hypertension of the portal circuit with ascites, etc. In some instances, for unknown reasons, a recurrence of an acute hepatitis arises which rapidly results in death.

Whether carcinoma ever arises in such a liver is problematic because I have not been able to find a case in which such a transition was noted. That carcinoma arises in cirrhotic livers is well admitted, accounting for the majority of reported primary carcinomata of the liver, and the carcinomata of the liver arising in Chinese affected with clinorchis sinensis causing secondary hepatic cirrhosis.

THE BIOLOGY OF TOXIC HEPATITIS



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MASSIVE PULMONARY EMBOLISM, I*

BASED IN PART ON A STUDY OF EIGHTY-EIGHT FATAL CASES¹

HAROLD NEUHOF, M.D., AND SAMUEL H. KLEIN, Major, MC., A.U.S.²

A vast literature on the subject of pulmonary embolism attests to the fact that extensive clinical and experimental efforts have been devoted to various phases of the problem. Despite innumerable studies, pulmonary embolism remains an important and only partly solved cause of morbidity and mortality. It has been estimated (1) that more than 30,000 persons die from pulmonary embolism yearly in the United States.

The purpose of this contribution, made at the request of the Medical Board of The Mount Sinai Hospital, is twofold: first, to review the problem of pulmonary embolism in its various aspects, namely, the etiology, physiology, symptomatology, diagnosis and treatment; secondly, on the basis of a critical analysis of 88 consecutive fatal cases of proven pulmonary embolism, to attempt to formulate criteria for diagnosis, prophylaxis and treatment.

The 88 cases of fatal pulmonary embolism occurred in the period between January 1, 1927 and April 1, 1938. Since 1938 one surgical service at The Mount Sinai Hospital has consistently employed measures regarded as prophylactic with results which will be set forth. The diagnosis of pulmonary embolism was certified by post-mortem examination in all 88 cases. The clinical notes were derived from the records made on charts by nurses and by members of the attending, resident, and interne staffs. Information concerning the pathology was obtained from autopsy protocols.

The nurses' notes are of great importance and cannot be overlooked in attempting to reconstruct the clinical picture. In some cases in our series, nurses have recorded observations in great detail and in chronological order. Many of the manifestations of pulmonary embolism occur with the nurse as the sole observer, and the observation of a well-trained nurse can and should be relied upon. DeTakats and Jesser (2) have also called attention to the importance of the nursing records in these cases.

I. ETIOLOGY

A. Incidence. A survey of large collective statistics by DeTakats and Jesse (2) reveals a fairly consistent incidence of pulmonary embolism in large hospitals.

* This is the first installment of a series of seven articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting the second in the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

¹ From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital.

² Major Klein, adjunct surgeon to The Mount Sinai Hospital and now serving overseas with The Mount Sinai Hospital Unit, has contributed the study of the fatal cases and the analysis on which the work is based.

services, namely from 0.1 to 0.2 per cent of all operations, 2 per cent of all deaths, 6 per cent of postoperative deaths and about 10 per cent of all autopsies.

It should be kept in mind, however, that figures indicating the incidence of pulmonary embolism may at best be considered only an approximate rather than a true index. In view of the difficulties frequently encountered in evaluating the clinical picture (to which attention will be drawn) the erroneous diagnosis of pulmonary embolism undoubtedly is made at times in patients suffering from other conditions producing similar signs and symptoms. On the other hand, the existence of pulmonary embolism may be overlooked or be quite impossible of diagnosis in some cases. We have reviewed the autopsy records of a large number of cases and have noted the not infrequent discovery of pulmonary infarcts and even major emboli in the pulmonary arteries which were unsuspected

TABLE 1

Incidence of Massive Pulmonary Embolism in The Mount Sinai Hospital from 1927 to 1938

YEAR	ADMISSIONS	DEATHS	AUTOPSIES	VERIFIED FATAL P.E.	RECOVERED (UNPROVEN) SEVERE P.E.	FATAL P.E.; NO AUTOPSY VERIFICATION
1927	11,570	803	425	2		
1928	11,532	812	461	6		
1929	11,874	862	531	9		1
1930	11,650	809	506	9	1	2
1931	12,167	849	583	10	1	1
1932	13,689	805	473	4	3	2
1933	13,797	827	436	6	2	2
1934	14,198	838	382	8		2
1935	13,359	734	388	10		3
1936	14,749	828	398	8		
1937	15,745	866	451	13		
1938 (to April 1)	3,771	221	112	3		
	148,101	9254	5146	88	7	13

clinically. Churchill (3) also emphasizes that there is a well known discrepancy between the clinical diagnosis of pulmonary embolism and the autopsy findings and states that perhaps in no other condition do hospital statistics show a greater percentage of error.

Another source of statistical error arises from the failure to obtain permission for post-mortem examination in all cases. Thus, cases may be incorrectly classified as having died of pulmonary embolism in a classification based only on the clinical impression. In other cases, in which the diagnosis of pulmonary embolism may have been missed clinically, the true cause of death will never be recorded if an autopsy is not performed.

With these reservations in mind, we have determined the incidence of major pulmonary embolism in The Mount Sinai Hospital from 1927 to 1938 (Table 1). Since our analysis is concerned essentially with the fatal type of pulmonary em-

bolism, we have excluded all cases of minor embolism characterized by symptoms of pulmonary infarction as well as incidental infarctions which were not considered as contributing to death. As noted in Table 1 there were in addition to the 88 cases of fatal pulmonary embolism verified by autopsy 7 patients who recovered following severe clinical episodes which appeared to be characteristic of pulmonary embolism. In a third group of 13 cases, death occurred with clinical manifestations strongly suggestive of pulmonary embolism, but autopsies were not performed. Thus, the diagnosis of pulmonary embolism must be regarded as presumptive in the latter two groups of cases. The study to be presented will be based primarily on a consideration of the 88 verified cases, but the 20 additional cases will be referred to in the discussion.

If we include the presumed 13 fatal cases with the verified 88 fatal cases of pulmonary embolism, the incidence of fatal pulmonary embolism based on 148,101 hospital admissions is 0.068 per cent. Excluding the 13 fatal cases of embolism in which the diagnosis was not verified, the incidence is 0.059 percent. Based on the number of deaths during this period (9,254), the incidence of fatal pulmonary embolism is 1.09 per cent if both verified and unproven fatal cases are computed together, and 0.95 per cent if only the autopsied cases are considered.

B. Types of Cases in which Pulmonary Embolism Occurs. Despite evidence to the contrary there seems to remain a widely held impression that fatal pulmonary embolism is a complication restricted largely to postoperative or postpartum cases. White (4) states that pulmonary embolism has failed to attract the interest and attention it has deserved as an important complication of non-surgical or non-obstetric cases. There are many published statistics which establish that non-surgical patients are decidedly prone to develop pulmonary embolism.

Hultquist (5) and Meyer (6) found the frequency of death from embolism to be about the same in surgical services as in clinics for medical diseases. In a series of 567 autopsies, Belt (7) found 56 cases (6.5 per cent) in which pulmonary embolism was the cause of death. The ratio of medical to surgical cases in his series was 40:16. McCartney (8) reviewed 9,275 necropsy records and noted 73 cases in which death was due to pulmonary embolism. These cases were divided into four groups as follows:

- 1) A. Post traumatic—15 cases
- B. Post traumatic with operation in consequence of the injury—8 cases
- 2) Postoperative—31 cases (all these operations were below the diaphragm)
- 3) Post parturition—3 cases
- 4) Medical—16 cases.

Henderson's (9) post-mortem study of 313 cases of pulmonary embolism over a ten year period revealed that in 267 cases it was a postoperative complication. Forty-six were non-surgical cases. In 223 (83.5 per cent) of the 267 cases, emboli were the primary cause of death. In 44 (16.5 per cent), the emboli were either contributory factors or were so small that they had little or no connection with the fatal issue.

Pilcher (10) reported a series of 731 cases of fatal pulmonary embolism, culled from the records of twelve London hospitals for the decade 1925 to 1934. Five hundred and thirty-seven of these occurred after operation, 36 followed accidental injuries, and in 158 there was no history of trauma. Cleland (11) reported fatal pulmonary embolism complicating the following medical conditions: tuberculosis, pneumonia, typhoid fever, and Flexner dysentery. Hemmings (12) found the total incidence of post-delivery embolism in a series of 80,136 births to be 0.04 per cent. It has also been stressed by many authors that pulmonary embolism is a not uncommon complication in patients suffering from cardiac disease.

Table 2 summarizes the 88 fatal cases of pulmonary embolism verified by autopsy. There were 62 patients who had undergone operative procedures (58 patients had major and 4 had minor operations), and there were 26 non-operative cases. In the latter group there was one traumatic case, a compound fracture treated without operation. During the period covered by this study, there were treated in the hospital 1,264 cases of various types of fractures, but there were only two instances of fatal pulmonary embolism verified by autopsy. One of these was the case noted above and the other (presumptive) was a fracture of the neck of the femur treated by the insertion of Kirschner fixation wires.

Barker, Nygaard, Walters and Priestly (13), in a statistical study of the incidence of postoperative venous thrombosis and pulmonary embolism after various types of operation, indicated that these complications are more common following 1) types of laparotomy in which operations on the female pelvic organs are done with possible injury to or ligation of branches of the iliac veins; 2) operations of long duration and of great magnitude in which considerable tissue is removed and in which there is likely to be further tissue injury; and 3) cases in which there is infection.

Giertz and Crafoord (14) also found that pulmonary embolism was more common in patients who had had some operation below the diaphragm than above it, and that those subjected to laparotomy were most likely to be affected. This is also true in our series.

The susceptibility to pulmonary embolism of patients who have undergone laparotomy may be the result of one or more factors, according to arguments advanced by many authors. It is maintained that in pelvic operations, trauma to the large plexuses of veins may initiate thrombus formation in this area. Venous stasis with subsequent thrombosis of veins in the pelvis and lower extremities may be produced by tight abdominal dressings and binders, as well as by the restriction of thoracic and abdominal respiratory movements due to pain with resultant reduction of the suction-like effect of deep breathing on the venous circulation. The bed rest generally given to patients who have had abdominal operations in itself may invite thrombosis on the basis of stasis in the large veins of the pelvis and lower extremities.

Since pulmonary embolism occurs after minor operative cases and in medical cases it is obvious that other factors, not dependent upon operative trauma, must be involved in the mechanism of thrombosis with subsequent embolism. These will be discussed in succeeding sections.

TABLE 2

Summary of 88 fatal cases of pulmonary embolism verified by autopsy

CASE NO.	MALE	FE-MALE	AGE	OBESE	NOT OBESE	DIAGNOSIS	OPERATION
1	✓		70		✓	Carcinoma of the sigmoid colon with cul-de-sac metastases.	Caeceostomy. Exploratory laparotomy.
2		✓	41		✓	Fibromyomata of uterus.	Supravaginal hysterectomy. Right salpingo-oophorectomy.
3		✓	55	✓		Acute appendicitis.	Appendectomy.
4	✓		80		✓	Fracture of neck of left femur.	1. Reduction of fracture. Insertion of Kirschner wires. 2. Secondary reduction of fracture.
5	✓		45	✓		Seminoma of testis.	Orchidectomy.
6		✓	48		✓	Chronic glomerulonephritis. Generalized anasarca.	
7	✓		22		✓	Acute appendicitis. Generalized peritonitis.	Appendectomy.
8		✓	52	✓		Diabetes mellitus. Carcinoma of transverse colon.	Partial colectomy with side-to-side anastomosis.
9	✓		45		✓	Thrombo-angiitis obliterans. Coronary artery disease. Myocardial insufficiency.	
10		✓	57		✓	Fibromyomata of uterus (with malignant degeneration). Adenocarcinoma of rectum.	Rectal biopsy.
11		✓	52	✓		Chronic cholecystitis with common duct calculus. Diabetes mellitus	Choledochostomy.
12		✓	71	✓		Postoperative incisional hernia.	Hernioplasty.
13	✓		60		✓	Gastric ulcer.	Exploratory laparotomy.
14		✓	55	✓		Right renal and ureteral tuberculosis.	Right nephrectomy and partial ureterectomy.
15		✓	60		✓	Bilateral chronic pyelonephritis with abscesses.	
16		✓	52	✓		Perforated sigmoid diverticulitis.	Partial colectomy.
17	✓		42	Not noted		Acute appendicitis.	Appendectomy.
18		✓	40	✓		Cystocele and rectocele. Fibromyomata of uterus.	Supravaginal hysterectomy. Bilateral salpingo-oophorectomy. Colporrhaphy.
19		✓	45	✓		Chronic rheumatic cardiovascular disease. Mitral stenosis and insufficiency.	
20	✓		68	✓		Acute appendicitis with abscess. Old coronary thrombosis.	Drainage of appendix abscess.

TABLE 2—Continued

CASE NO.	MALE	FE-MALE	AGE	OBESE	NOT OBESE	DIAGNOSIS	OPERATION
21		✓	43	✓		Fibromyomata and myosarcoma of uterus.	Supravaginal hysterectomy, and bilateralsalpingo-oophorectomy.
22	✓		47		✓	Bilateral inguinal herniae.	Hernioplasty (attempted pulmonary embolectomy).
23		✓	32		✓	Pulmonary tuberculosis. Pleurisy with effusion.	
24		✓	37	✓		Right ovarian cyst. Bronchial asthma.	Resection and marsupialization of ovarian cyst.
25		✓	70	✓		Acute purulent bronchitis.	
26		✓	51	✓		Acute pyelonephritis and ureteritis.	
27		✓	30		✓	Cystocele and rectocele. Suburethral cyst. Fibromyomata of uterus. Cyst of ovary. Chronic appendicitis.	Anterior and posterior colporrhaphy. Excision of ovarian and suburethral cysts. Myomectomy. Appendectomy.
28		✓	75	✓		Arteriosclerotic cardiovascular disease. Metabolic nephrosis.	
29		✓	48	✓		Suppurative cellulitis of foot. Diabetes mellitus.	Incision and drainage.
30		✓	50	✓		Postoperative incisional hernia.	Hernioplasty.
31		✓	49	✓		Inguinal hernia. Dyskeratosis of labium.	Hernioplasty. Excision of labium.
32		✓	47	✓		Abscess of ankle.	Incision and drainage.
33		✓	49	✓		Acute appendicitis. Diabetes mellitus.	Appendectomy.
34	✓		36		✓	Acute appendicitis.	Appendectomy.
35	✓		50	Not	noted	Subdural hematoma. Meningioma.	Ventriculogram. Right frontal craniotomy.
36		✓	26		✓	Lupus erythematosus. Verrucous endocarditis.	
37	✓		61		✓	Carcinoma of the rectum with metastases.	Exploratory laparotomy. Colostomy.
38		✓	54	✓		Hypertensive cardiovascular disease.	
39		✓	58	✓		Meningeal fibroblastoma.	Craniotomy and excision of tumor.
40		✓	57	✓		Diabetes mellitus. Acute appendicitis with abscess.	Appendectomy with drainage.
41		✓	62		✓	Pernicious anemia. Acute pyelonephritis.	
42		✓	58	✓		Carcinoma of the colon.	Caecostomy.

TABLE 2—Continued

CASE NO.	MALE	FE-MALE	AGE	OBESE	NOT OBESE	DIAGNOSIS	OPERATION
43	✓		56		✓	Acute appendicitis.	Appendectomy with drainage
44	✓		73	✓		Carcinoma of the sigmoid colon with obstruction.	Transverse colostomy.
45		✓	37		✓	Carcinoma of the ovary with metastases.	Exploratory laparotomy.
46	✓		51		✓	Carcinoma of the liver.	
47	✓		80		✓	Arteriosclerotic gangrene of the foot.	
48	✓		40	✓		Carcinoma of the stomach with metastases.	
49	✓		65	Not noted		Umbilical hernia with strangulated omentum.	Hernioplasty and resection of omentum.
50	✓		45	✓		Right inguinal hernia.	Hernioplasty.
51	✓		62		✓	Acute appendicitis.	Appendectomy with drainage.
52		✓	60	✓		Diabetes mellitus. Gangrene of foot	Mid-thigh amputation.
53	✓		65	✓		Carcinoma of the sigmoid colon.	Partial colectomy and colostomy.
54		✓	70	✓		Hemiplegia.	
55	✓		63	✓		Ureteral calculi. Hypertrophied prostate.	Ureterolithotomy. Suprapubic cystostomy.
56	✓		56		✓	Detachment of the retina.	Safar operation.
57		✓	53		✓	Ovarian carcinoma.	Supravaginal hysterectomy. Bilateral salpingo-oophorectomy.
58	✓		65		✓	Carcinoma of the prostate with urinary obstruction.	Bilateral vas ligation. Transurethral prostatic resection.
59	✓		40		✓	Right inguinal hernia.	Hernioplasty.
60	✓		64	✓		Chronic ulcerative esophagitis with hemorrhage.	
61	✓		59	✓		Brain tumor.	
62		✓	65	✓		Carcinoma of the rectum.	Partial colectomy. Colostomy.
63		✓	65		✓	Carcinoma of the ovary with generalized carcinomatosis.	Exploratory laparotomy.
64	✓		60		✓	Hypertrophied prostate. Rheumatic cardiac disease.	Bilateral vas ligation. 2-stage suprapubic prostatectomy.
65	✓		72		✓	Hypertrophied prostate.	Bilateral vas ligation.
66		✓	75		✓	Coronary artery disease.	
67	✓		44	✓		Coronary artery disease.	
68	✓		62		✓	Lobar pneumonia.	

TABLE 2—*Concluded*

CASE NO.	MALE	FE-MALE	AGE	OBESE	NOT OBESE	DIAGNOSIS	OPERATION
69	✓		55		✓	Gastro-jejunal ulcer.	Partial gastrectomy.
70		✓	68	✓		Nephrolithiasis and perinephric abscess.	Pyelolithotomy and renal decapsulation.
71	✓		36		✓	Pulmonary tuberculosis with esophageal fistula.	
72	✓		52		✓	Carcinoma of the stomach with hepatic metastases.	Exploratory laparotomy.
73	✓		70	✓		Hypertrophied prostate. Diverticulum of the bladder.	1. Suprapubic cystostomy. Resection of diverticulum. 2. Left renal decapsulation for urinary suppression.
74	✓		53	✓		Compound fracture of tibia and fibula.	
75	✓		45		✓	Acute appendicitis with peritonitis.	Appendectomy with drainage.
76	✓		77		✓	Atherosclerotic cardiovascular disease with heart block.	
77	✓		64		✓	Coronary artery disease. Cerebral thrombosis.	
78		✓	54	✓		Chronic cholecystitis and cholelithiasis.	Cholecystectomy.
79		✓	48	✓		Fibromyomata of uterus. Cystocele.	Supravaginal hysterectomy. Anterior colporrhaphy.
80	✓		48	✓		Endocrine obesity. Bronchiectasis.	
81		✓	60	✓		Chronic cholecystitis and cholelithiasis.	Cholecystectomy.
82		✓	49	✓		Carcinoma of the stomach.	Partial gastrectomy.
83		✓	59	✓		Carcinoma of the gall bladder with hepatic metastases.	Exploratory laparotomy.
84	✓		61		✓	Carcinoma of the rectosigmoid colon.	Abdomino-perineal excision.
85	✓		54		✓	Hypertrophied prostate.	Suprapubic cystostomy. Bilateral vas ligation.
86	✓		69		✓	Hypertrophied prostate.	
87		✓	60		✓	Acute pancreatitis.	Cholecystostomy.
88		✓	48		✓	Chronic ulcerative proctitis with multiple fistulae.	Transverse colostomy.

Barker (quoted by Barnes (1)) noted that malignancy was present in a large number of his cases of fatal pulmonary embolism (42 per cent) and that this percentage was out of proportion to the total number of patients who underwent

operation. In our series, the group of 62 operative cases included 19 cases of malignancy (including one brain tumor). There were 3 cases of malignant neoplasm (including one brain tumor) in the non-operative group. Thus, it would seem that in addition to other factors contributing to thrombosis, the debility and cachexia of malignant disease plays a rôle in the circulatory changes involved in the initiation of thrombosis.

C. Seasonal Incidence. A difference of opinion in the literature regarding the influence of season and weather upon the incidence of pulmonary embolism is evidence of a groping effort to discover some significant causative factor.

Cleland (11) found no evidence that pulmonary embolism was more likely to occur in any particular season of the year, or that cases occurred in groups ascribable to some common factor. Pilcher's (10) tables showed no seasonal

TABLE 3
Seasonal distribution

	JAN.	FEB.	MARCH	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	TOTAL
1927				1						1			2
1928		1				2					1	2	6
1929	1	2				2	1			1		2	9
1930		1			3			3	1			1	9
1931	1			1	2						3	3	10
1932	1				1				1			1	4
1933			3			1		1				1	6
1934	1		1		2		1	2		1			8
1935	1	2	3	1			1			1		1	10
1936	1			1	1		3		1			1	8
1937					2	1	1	4	2	1	1	1	13
1938*	2		1										3
Total	8	6	8	4	11	6	7	10	5	5	5	13	88

* To April 1.

or epidemic incidence, nor did the statistics of Domrich (15) and Domrich and Wagemann (16). Hultquist (5) also found no relationship. He noted fluctuations in mortality frequency with minimums in May and September and maximums in April, August, and October, and ascribed these findings to variations in the composition of the patient "material." Table 3 has been prepared to show the seasonal distribution of our series. It may be noted that the highest total monthly incidence occurred at both extremes of season, namely 8 cases in January, 13 in December, 11 and 10 cases in May and August respectively, with between 4 and 8 cases in each of most of the other months of the year. When one analyzes the monthly figures for each year, there seems to be no definite pattern of seasonal incidence in this series. It can be noted, however, that fatal pulmonary embolism occurs in this table in groups of 2, 3 or 4 cases per month, with many months in which it does not occur at all.

In this connection, DeTakats, Mayne and Peterson (17) scrutinized ten yearly

raphs in which the occurrence of pulmonary embolism was plotted against meteorologic factors such as wind, sunshine, barometric pressure, temperature, and precipitation. In this study embolism was most frequent from January to May and in the October to November periods. These authors state that, other factors being equal, a sudden meteorologic change is capable of precipitating vascular changes producing thrombosis and embolism.

D. Age and Sex Incidence. Table 4 shows the age and sex incidence in our series. These figures are in agreement with most of the published statistics which indicate that the greatest proportion of fatal pulmonary embolism occurs in the later decades of life, from 40 to 70 years. The age of our youngest patient was 22 years; that of the oldest, 80 years. In our series both sexes were almost equally affected; 43 males and 45 females.

In Henderson's (9) series of 313 cases of fatal pulmonary embolism there were 104 males and 119 females. The average age of the patients was 53.2 years. The average age of 1000 adult patients operated upon consecutively was 42.8

TABLE 4
Sex and age distribution

	YEARS							Total
	20-29	30-39	40-49	50-59	60-69	70-79	80-89	
Male	1	2	10	9	14	5	2	43
Female	1	4	12	15	8	5	0	45
Total	2	6	22	24	22	10	2	88

years. Thus the average age of patients dying from pulmonary embolism was 50.4 years greater than that of the average patient coming to operation.

McCartney (8), however, states that age is probably not as important a factor as it is generally thought to be, for when considered in relation to the number of necropsies done in each decade, his series revealed about the same incidence of embolism in all decades after the first.

Barker and his associates (18) showed that although the relative incidence of all thromboses and embolisms was greater in women than in men (series of 1,665 consecutive cases of postoperative venous thrombosis and pulmonary embolism following 172,888 operations), the incidence of pulmonary embolism, both fatal and non-fatal, was greater in men. The age of their youngest patient with fatal pulmonary embolism was 20 years. Hultquist (5), on the other hand, reported that women were more disposed than men to pulmonary embolism, the difference being especially marked in fatal embolism (stasis in varicose veins?).

Aside from the factor of pelvic trauma, incident to gynecologic and obstetric procedures, there appears to be no other underlying physiologic mechanism in the female to account for an increase in susceptibility to thrombosis and embolism.

The preponderance of thrombo-embolic disease in middle-aged and elderly

patients may perhaps be explained by the fact that a large proportion of hospital patients fall into this age group and also that debilitating conditions productive of the various factors contributing to venous stagnation and thrombosis occur more frequently in older people. Nevertheless, it must not be overlooked that pulmonary embolism can and does occur in young and vigorous persons.

E. Obesity. It was surprising to note in our series that the factor of obesity was not as obvious as would be anticipated from the literature. Only 44, or one-half of the total of 88 patients, were classified as obese (Tables 2 and 5). Of the remaining 44 patients, 21 were noted to be "well developed and nourished," and 16 were thin and even emaciated. Most of the latter were suffering from neoplastic disease.

On the basis of careful records of the weight of their patients, Giertz and Crafoord (14) venture to say that the obese are by no means more predisposed to thrombo-embolic disease than are thin patients. In their series, 63 patients were obese and 176 were thin. In view of this great difference they state, "obesity is of no decisive importance in the development of thrombo-embolic disease." On the other hand, Barker et al. (18) state that postoperative throm-

TABLE 5
Classification of Physical Habitus

Thin or emaciated	16 cases
Well developed and nourished	21 cases
Obese	44 cases
Habitus not noted	7 cases

bosis and pulmonary embolism are definitely though not markedly more common in obese than in non-obese patients. Collins (19), Russum and Kemp (20), Hultquist (5), and others believe that obesity is an important factor in the etiology of pulmonary embolism.

Most of Henderson's (9) 313 cases of fatal pulmonary embolism were somewhat over-weight. Snell (22) noted that pulmonary embolism following operation seems to be a more common cause of death of the obese patient than of the average patient. From a consideration of the statistics, he states that it seems probable that there is a group of patients about 50 years of age, obese, and with normal or subnormal blood pressure, who are particularly susceptible to pulmonary embolism as a postoperative complication.

To be continued

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LIFE'S LATER YEARS

STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[New York City]

PART 1*

"From history we have to learn not only what our ancestors conceived, and made, but also why they thought and acted so. For if the world-drama is, in part, of man's conflicts with nature, it is far more a drama of his conflicts with his kind and with himself."

Sir Clifford Allbutt—Greek Medicine in Rome

INTRODUCTION

The story of man's struggle against old age and its maladies is a significant but rarely differentiated part of medical history. Since the tremendous advances of the last century in increasing the expectancy of human life have forcibly brought the problems of the advancing years to the attention of the practising physician, he must seek a sound foundation for present day thinking in a clear realization of the historical perspective. He must look back over several thousand years, follow carefully the devious paths of superstition, folk-belief, magic and religion to trace the uneven progress of medicine until the relatively recent development of a scientific viewpoint is finally attained. Contact with the great minds of the past, whose thoughts and observations are so often remarkably fresh and unimpaired by time, will bring the humility that history alone can teach.

Old age in its relation to medicine is a part of that larger field of inquiry, old age and society, consideration of which must be deferred until the time when the social implications of old age may be taken up as a whole. For the present our concern is limited to the theories and practices of priests, magicians, philosophers and physicians, as related to aging man and his diseases. We shall find that some of the most notable contributions in the past have been made by individuals entirely untrained in the healing art. Of the three most famous descriptions of advanced age, one is attributed to an unnamed preacher, and two have emanated from great poets. During the Renaissance many great thinkers turned their attention to the problem, but the widest influence was exercised by a reformed rake, whose theory of longevity through undernutrition was dramatically demonstrated by his actually living past the century mark. In our own time real leadership has often been found in the teachings of the biologists; unusual insight and objectivity were combined in the last work of a great psychologist. On the other hand, the bulk of the investigative endeavor, to say nothing of the diag-

* This is the first in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting the third in the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

nostic and therapeutic responsibility, has been in the hands of the medical profession. These instances of lay participation serve notably to illustrate the intense preoccupation of all mankind with our problem which, in the words of Dawson (1), forms "the history of human effort to prolong life and avert extinction—an effort out of which the magician, priest and doctor had their origin."

PRIMITIVE MAN

The skeletal anatomy of the early races of man has been carefully studied in the scanty material made available by the archeologists. On the basis of field and laboratory studies, definite time and cultural correlations have been set up. Professor Krogman's chart of the Pleistocene Period (fig. 1), shows vividly many essential features of the life and the culture of primitive man.

The recent work of Vallois (2) and Weidenreich (3) now furnishes interesting, although meager data as to the longevity and pathology of early and late Paleolithic man. The age determinations are largely based on the times of closure of various skull sutures (4). The first mentioned investigator studied the remains of Neanderthal man, and concluded that his life duration was very brief, inasmuch as out of 20 individuals only 5 per cent reached an age of more than 40 years, while 40 per cent died as children of 11 years or less. Late Paleolithic man, in contrast, shows a distinct lengthening of his life, 10.8 per cent of the individuals reaching an age of 40 and 1 per cent even more than 50 years, whereas the percentage of children dying before 11 years decreases to 24.5 per cent.

In the series of *Sinanthropus* bones reported by Weidenreich, numbering 38 persons, 15 or 39.5 per cent were children 14 years or less, judging by dentition; 3 skulls may have belonged to individuals less than 30 years old, 3 may have ranged between 40 and 50 years, and only 1, apparently that of a woman, of whom unfortunately only small fragments remain, may have been 50 or even 60 years of age. The location of the remains in the famous cave at Choukoutien, near Peiping, indicate that the existence of these people must be dated back at least 25,000 years, probably even more. Late Paleolithic man, as compared with *Sinanthropus*, is represented by only 7 individuals, 3 definitely juvenile, 4 adults, of whom 2 were probably women slightly over 20, the age of the third being indefinite, but not old. The fourth adult was certainly an old man of at least 60 years. These figures for the East are to be compared with Vallois' for the Western parts of the old world. In both the *Sinanthropus* and the later Paleolithic series from the East, all died violent deaths from skull injuries.

These contributions are quoted in detail to bring out that there *seems* to be evidence for a difference between early and late Stone Age life duration based on the examination of actual remains, and that anatomical findings point to few individuals reaching an advanced age. Such scanty data can at best be hardly more than suggestive. Vallois believes that the more refined civilization of later Paleolithic time permitted survival of individuals who under the coarser conditions of more primitive living would surely have been exterminated. Weidenreich is of the opinion that primitive man, like undomesticated animals, had

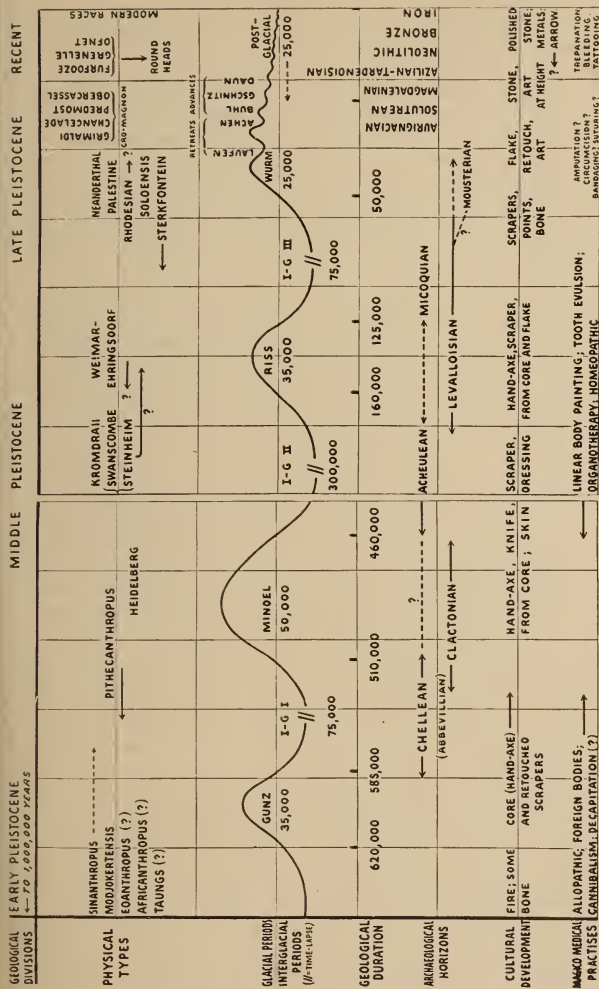


FIG. 1. The Pleistocene History of Man and His Culture (after Daly, Nelson, Zeuner). (From W. M. Krogman, The Pathologies of Pre- and Protolithic Man, Ciba Symposia, Vol. 2, No. 2, May 1940. Reproduced by permission of Ciba Symposia and Prof. Krogman).

greater resistance to infectious disease in general. He calls attention to the attrition of teeth due to the coarse diet, to the total absence of signs of dental caries or pyorrhea alveolaris, and finally to the osteoarthritic changes in the vertebrae of the old man in his late series (5).

The bare bones of ancient peoples (6), while yielding much valuable information as to the size and the shape of the brain and the relative proportions of its component parts, give us but little insight into their actual mental processes and customs. For this information we turn to comparative anthropology, which is concerned with the study of so-called savage peoples living today, or in the recent past, whose cultural development is thought to approximate that of our Stone Age ancestors. The study of folk-lore throughout the world, in civilizations of all degrees of complexity, has likewise thrown much light on primitive patterns of thinking.

In his monumental work "Folkways," Sumner (7) devotes a whole chapter to the consideration of abortion, infanticide and killing the old, pointing out that the rearing of children and the caring for the weak were, under rigorous conditions of living, burdens that required summary action from the standpoint of group welfare. He describes "two sets of mores as to the aged: (a) in one set of mores the teaching and usages inculcate conventional respect for the aged, who are therefore arbitrarily preserved for their wisdom and counsel, perhaps also sometimes out of affection and sympathy; (b) in the other set of mores the aged are regarded as societal burdens, which waste the strength of society, already inadequate for its tasks. Therefore they are forced to die either by their own hands, or those of their relatives." Abundant ethnographic illustrations are given of both viewpoints. Civilized men face to face with primitive conditions may find their sentiments temporarily overcome by grim necessity. Sumner emphasizes that with the improvement of living conditions there was less and less necessity for doing away with the weak, and in borderline cases men would be apt to be swayed by repugnance of the act rather than by the dislike of hardship. He points out that a kindly sentimental attachment to the old is a product of civilization, possible only to men for whom the struggle and competition of life had become definitely moderated. One need hardly be reminded that even today these primitive attitudes keep coming to the fore, and have formed an intrinsic part of the political program of the most bestial scoundrels who have ever sought to enslave the world.

Dawson (8) has emphasized that "primitive man was not an abstract thinker and long ages had elapsed before he had accumulated the knowledge necessary to convince him that death is the inevitable fate of all living creatures." To the mitigation of this fate primitive religion devoted itself, for in many lands and among many peoples we find the concept that death is the result of avenging spirits or gods, and that in the beginning of the world man was immortal. Innumerable legends and myths have arisen to explain the origin of old age and death, all of which embody the same basic ideas with varying amounts of elaboration. Many are based on the forbidden fruit theme exemplified by the Biblical story (9), and on the punishment resulting from disobeying the instructions of

the deity. Others have to do with the casting off of the skin. Savages had naturally observed the periodic renewal of the surface coverings of snakes, lizards, crabs and beetles, with their apparent rejuvenation following this process. The far-reaching meaning of this natural process for the primitive mind is attested by the illuminating observation of Richardson (10) that "in both Greek and Latin the words for old age, γῆρος and *senectus*, are used to designate the casting off of the skin of an animal." Philology thus confirms the intimate association of the ideas of old age and rejuvenation by prehistoric man.

It will be recalled that in Greek mythology the snake is the symbol of rejuvenation and was intimately associated with Asklepios, the god of healing. While his property of the snake plays no rôle in the Biblical story of the Fall of Man, the choice of this animal as the villain of that piece is not accidental, and in Frazer's opinion indicates the essential unity of the two fundamental themes.

"The Arawaks of British Guinea say that man was created by a good being whom they call Kurunumany. Once on a time this kindly creator came to earth to see how his creature man was getting on. But men were so ungrateful that they tried to kill their Maker. Hence he took from them the gift of immortality and bestowed it on animals that change their skins, such as snakes, lizards and beetles. Again, the Tamanachiers, an Indian tribe of the Orinoco, tell how their creator kindly intended to make man immortal by telling them that they should change their skins. He meant to say that by so doing they should renew their youth like serpents and beetles. But the glad tidings were received with such incredulity by an old woman that the creator in a huff changed his tune and said, 'Ye shall die!' " (11)

Having once lost the gift of immortality, the efforts of mankind in the form of religion were designed to propitiate the gods, in order to prolong life and to avert bodily sufferings whether due to injury or disease. This last mentioned distinction, when finally achieved, represents one of the greatest of advances in the medical thinking of all time. That external violence could cause pain, raise a swelling, break a bone or even kill was an actual commonplace of primitive experience, but for long ages all other forms of bodily suffering were ascribed to supernatural causes. "What we call natural death is nearly always attributed to witchcraft, sorcery or divine interference in human affairs. Such are the prevailing ideas among primitive peoples today, and by analogy, such was probably the belief of primitive man before the advent of civilization." (Dawson).

An additional fact of primitive experience was the association of advancing years with the diminution of bodily powers, the loss of sexual attractiveness, and increased likelihood of death. Here, too, the myths attempt to explain away reality, and primitive religion holds forth the hope of a better life to come. Malinowski's studies among the Trobriand Islanders, inhabiting a part of British New Guinea in Northwestern Melanesia, furnish enlightening detail and explanation on these points. These quotations from his work bear also on the preceding discussions.

"To enjoy life and love it is necessary to be young. Even in Tuma (paradise), old-age, that is, wrinkles, grey hair and feebleness, creeps from the

spirits. But in Tuma there exists a remedy, once accessible to all mankind, but now lost to the world. For old age to the Trobrianders is not a natural state—it is an accident, a misadventure. Long ago, shortly after mankind had come upon the earth from underground, human beings could rejuvenate at will by casting off the old withered skin; just as crabs, snakes and lizards and those creatures that burrow underground will every now and then throw off the old covering and start life with a new and perfect one. Humanity, unfortunately, lost this art—through the folly of an ancestress, according to legend—but in Tuma, the happy spirits retained it. When they find themselves old, they slough off the loose, wrinkled skin, and emerge with a smooth body, dark locks, sound teeth and full vigor. Thus life with them is an eternal recapitulation of youth with its accompaniment of love and pleasure.” (12)

“Old age is felt to be a serious handicap in affairs of gallantry. The contrast between repulsive old age and attractive youth is brought out clearly in the myth. A hero, who is unsuccessful because of his elderly appearance, becomes rejuvenated and gets everything he wants. First, the marks scored upon him by the hand of time are ruthlessly enumerated: a wrinkled skin, white hair and toothless jaws. Then the magical change is described: his rounded face, the smooth full lines of the body, his sleek glossy skin, the thick black hair covering his head, the beautiful black teeth showing between vermilion lips. Now he can win the favors of desirable women and impose his wishes on men and Fate. Such pictures are drawn in two of the chief myths of the Kula (the ceremonial interchange) which plays such a great part in tribal life and shows so many psychological affinities to their erotic interests. Similar pictures are also to be found in the ideas of the natives concerning a future life and in one or two fairy tales.” (12)

In drawing the picture of primitive man's attitude toward his environment, his fellows and to himself, we have spoken chiefly of religion, which may be defined here as the belief in the control of man's destiny by higher powers whose favor and good-will must be cultivated. Closely linked with it and perhaps preceding it historically, are the rites which today we call magic; rites in which incantations appropriate to the occasion and the purpose are recited, and certain definite manual activities performed, in order to bring about a desired result, usually without appeal to higher beings. Frazer has differentiated two varieties of magic, the *contagious*—according to which special properties are ascribed to objects once in contact with an object or thing, or which once formed part of it; the *sympathetic*—according to which magical effects may be projected at a distance, and also may be produced for good or evil by working upon objects of similar appearance. In the earliest times the treatment of diseases and injuries was in the hands of the priest-magician, who thus became in effect priest-magician-physician. The history of medicine, of human culture in fact, is concerned with the gradual differentiation of these three functions.

Today, according to Rivers (13), “medicine, magic and religion are abstract terms each of which connotes a large group of social processes, processes by means of which mankind has come to regulate his behavior towards the world

ound him. Among ourselves these three groups of processes are more or less arply marked off from one another. One has gone altogether into the back-ound of our social life, while the other two form distinct social categories idely different from one another and having few elements in common. If we rvey mankind widely this distinction and separation does not exist. There e many peoples among whom the three sets of social process are so closely terrelated that the disentanglement of each from the rest is difficult or impos-ble; while there are yet other peoples among whom the social processes to which



FIG. 2 Pottery Portrait of an Old Woman. This wrinkled, round face, with button nose and toothless mouth adorns a pottery vase which was found on the coast of Northern Peru by the sons of the Vice-President of Peru, Senor don Rafael Larco Herrera. This remarkable art work is a product of Cupisnique Indian culture, probably the earliest settlers in Peru, long antedating the Incas. (Reproduced by permission of Science News Service, from Science News Letter, November 15, 1941).

we give the name of medicine can hardly be said to exist, so closely is man's attitude toward disease identical with that which he adopts towards other classes of natural phenomena."

We shall find, as we proceed in our depiction of old age, that of all the stages of human life to which the physician devotes his attention, it has longest remained an equally anxious concern of the priest and to some degree also of the magician. That such is even today evident is to be explained by the biological limitations of the healing art. Throughout the centuries there has, therefore, been a struggle between the three forces, with the physician attaining the ascend-

ancy during the classic period of Greek medicine, the priest again domina during the Middle Ages, and in our own time a brief resurgence of the magici in the form of "spiritualism" and in pseudo-scientific efforts at rejuvenation.

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 KROGMAN, W. M.: *The Skeletal and Dental Pathology of an Early Iranian Site*. *Bull. Hist. Med.*, 8 (1): 28, 1940.
- (6) See among others: SIR ARTHUR KEITH: *New Discoveries Relating to the Antiquities of Man, The Interpretation of Brain Casts*. New York, W. W. Norton, Chapter 31, 1932.
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- (8) DAWSON, *op. cit.*
- (9) *Genesis 3: 1-24*. For an illuminating study of this passage see Sir J. G. FRAZER: *Folk-Lore in the Old Testament*, London, Macmillan & Co., 1: 70, 1919.
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Samuel H. Geist

July 1, 1885–December 14, 1943

In the death of Dr. Samuel H. Geist, a truly remarkable career came to an untimely close.

Dr. Geist was born in New York City, the son of Ralph Roger and Frances (Davis) Geist. Upon completion of his course at the College of the City of New York in 1904, he entered the College of Physicians and Surgeons of Columbia University, receiving his medical degree in 1908. A two year internship at The Mount Sinai Hospital was followed by a residency in obstetrics at the New York Lying-in Hospital. From 1911–12 he studied abroad at the University of Freiburg, where his work in clinical gynecology and obstetrics aroused his interest in gynecological pathology.

Returning to New York in 1912 he joined the staff of The Mount Sinai Hospital, an association characterized by his full and undivided allegiance for 31 years. After seven years as Adjunct Attending Gynecologist, he became Associate Gynecologist and in 1937, Gynecologist to the Hospital. During this time, or a period of twenty years, he served also as Associate in Surgical Pathology.

Dr. Geist was a Fellow of the New York Academy of Medicine, a member of the New York Pathological Society, a Fellow of the American College of Surgeons, a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the New York Obstetrical Society, a Fellow of the American Gynecological Society, and Clinical Professor of Gynecology at Columbia University.

During World War I, Dr. Geist served with The Mount Sinai Hospital Unit, U. S. Base Hospital #3, in Montpon, France. He worked untiringly in general surgery, and in addition, carried out various assignments calling for particular adaptability and administrative efficiency. His personality and gynecologic experience were not long hidden from the neighboring population, and his efforts in their behalf were an important factor in cementing relations between the local people and our hospital.

The scientific contributions made by Dr. Geist earned the acclaim of gynecologists and obstetricians throughout this country. His writings were numerous, original, often fundamental, and indicated a varied and intense scientific curiosity. Aside from monograph and special articles, his collected papers number well over one hundred. This marked productivity was a natural result of his exuberant energy and scientific enthusiasm.

Dr. Geist was equally well known as clinician, pathologist and endocrinologist. The plastic technic for the formation of an artificial vagina developed by him in collaboration with Dr. Robert T. Frank, has become a widely accepted operative procedure. His early investigations concerned with the morphology of menstrual blood and its diagnostic significance have been quoted extensively. Dr. Geist was one of the first in this country to contribute to a better understanding of theca cell tumors of the ovary. The histogenesis, pathology and biologic sig-



Samuel H. Geist

ificance of the endocrine tumors of the ovary were the subject of many of his papers. His exhaustive investigations of the effects of androgens in women, of implanted estrogens, and many other phases of gynecologic endocrinology were significant contributions. One of his last achievements, the result of ten years of painstaking labor, was the publication in 1943 of his book on Ovarian Tumors. As expressed in a review by a leading gynecologist, "This book goes a long way to being the perfect reference book and should be near the clinician's desk and the pathologist's bench."

As a physician, Dr. Geist possessed a combination of qualities rarely found in one individual. His keen insight into human problems, his surgical dexterity and profound knowledge of his specialty, his personal charm and manifest interest in his patients' welfare, all contributed to the great esteem and affection in which he was held by them.

As a preceptor, he was thorough, earnest, and dynamic. He sought always to give his staff every available opportunity for increasing their surgical experience. Though a hard task master at times, his drive and organizing ability were largely responsible for the large quantity and high quality of work produced by members of the group which he headed as Attending Gynecologist.

Dr. Geist found a haven of rest, relaxation, and love in his home with his extremely devoted wife and daughter. He occasionally mentioned the hope that when all his work was completed at the hospital he would retire to some quiet secluded spot. Unfortunately, fate intervened to end his plans abruptly and took from our midst a true friend, a renowned physician of whom The Mount Sinai Hospital will always be proud.

JOSEPH A. GAINES

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Diagnosis of the Etiological Factors in Female Sterility. I. C. RUBIN. Bull. New York Acad. Med., 18: 537, August 1942.

In general inquiry of a sterile mating include the following steps: 1) A complete medical history especially detailed in the sphere of genital function and the constitutional state. 2) General physical examination with particular reference to that of the genitals and secondary sex characters. 3) The Huhner test and if necessary examination of the unmixed semen. 4) Tubal patency test. 5) Urinalysis; blood examination including serologic tests for syphilis. 6) Basal metabolic rate determination and 7) in individual cases as the indications arise, further investigation by means of specialized tests including serologic, hormonal, roentgenologic and biochemical.

The clinical appraisal of the patient including her psychic peculiarities, domestic happiness, dietary habits and sex habits underlying her inability to conceive must continue to receive first consideration while laboratory methods judiciously applied as in other fields of medicine may serve as useful aids.

Progress in Myomectomy. I. C. RUBIN. Am. J. Obst. & Gynec. 44: 196, August 1942.

Myomectomy was begun a little over one hundred years ago as a bold surgical venture for the removal of a pedunculated tumor which was erroneously believed to spring from the ovary, and has gradually developed technically so that today multiple myomectomy is done as a conservative plastic operation upon the uterus with the specific object of not only removing all of the fibroids but of conserving the uterus with retention of menstruation and possible reproduction.

Hemorrhage is controlled by the use of an elastic rubber tourniquet circumscribing the cervix and constricting the uterine vessels on either side. This elastic tourniquet has made possible the bloodless removal of many fibroids which previously would have indicated hysterectomy.

Practically all intrauterine lesions are amenable to demonstration by means of radiopaque media injected into the uterine cavity. A viscous soluble crystalloid iodine solution has been found useful and safe and may replace diagnostic curettage. Uterine polyps may be removed by curettage and the polyp forceps, and submucous myomas may be removed by vaginal or abdominal hysterotomy at the same time as other fibroids are removed. If the operation is designed to relieve sterility the uterine incision and suture should guard against implicating the insertion of the Fallopian tubes.

Myomectomy is the ideal and at present the only conservative treatment for uterine fibroids which preserves menstruation and the possibility of reproduction.

Disease of Anorectum and Colon: Review of Certain Recent Contributions. R. TURELL. Am. J. Digest. Dis. 9: 248, August 1942.

In this paper the literature of proctoscopic and colonic disease appearing in 1941 was reviewed. New as well as established principles and procedures were included. The following subjects were discussed: neoplastic disease, diverticulitis and diverticulosis; diarrheas; tuberculosis; pruritus; actinomycosis; venereal diseases; hemorrhoids; anal

neotintence; foreign bodies; perforation of rectum and sigmoid; war wounds; chronic constipation; enterobiasis; pregnancy and anorectal lesions, and miscellaneous considerations.

Treatment of War Wounds of the Thorax. A. H. AUFSES. Am. Rev. The., 46: 111, August 1942.

The basic principles in the treatment of thoracic wounds are reviewed. General therapeutic measures and treatment of shock are itemized. Thoracic wounds are divided into those of 1) the chest wall; 2) the pleura with minor pulmonary damage and 3) with major pulmonary damage; 4) the heart and pericardium, and 5) combined thoracoabdominal injuries. Emergency methods, as well as immediate postoperative care and secondary operative procedures, are outlined. The paper does not go into detail; its purpose is to set forth the basic principles in the treatment of thoracic wounds. It is written to serve the physician, inexperienced in thoracic surgery, who may suddenly be called upon to treat civilian or military casualties.

Recurrent Rheumatic Endocarditis with Terminal Hyperpyrexia. W. H. Branch. J. N. M. A. 34: 194, September 1942.

A case of recurrent rheumatic endocarditis with terminal hyperpyrexia is presented because of its rarity.

A thirty-one year female had a fulminating course of fever, polyarthritis, anorexia, drenching sweats, and subcutaneous nodules on the hands and feet. Leucocytosis was present. Blood cultures were negative. Aortic insufficiency, mitral insufficiency and stenosis were present. The severe joint symptoms and depressed mental state were replaced by excitability with visual and auditory hallucinations.

Diuretics were given on several occasions for congestive heart failure.

Left sided hemiplegia occurred with aphasia preterminally.

Stupor appeared on the last day changing rapidly to coma.

The temperature rose to 109° F.

The heart slowed rapidly.

Death was probably of cerebral origin.

Multiple Myeloma with Unusual Visceral Involvement. J. CHURG AND A. J. GORDON. Arch. Path. 34: 546, September 1942.

A rare case of gross visceral involvement in the course of otherwise typical multiple myeloma is reported. The involvement was most striking in the spleen which was considerably enlarged and studded with round nodules composed of myeloma cells. Smaller nodules were also found in the lymph nodes and in the liver. The renal changes were typical of "myeloma kidney".

The myeloma cells resembled plasma cells in some and myeloblasts in other respects. On the basis of work of Naegeli and of Rohr, their origin is ascribed to the reticulum of the bone marrow. It is suggested that the relationship between multiple myeloma and myeloid leukemia may be analogous to that between lymphosarcomatosis and lymphatic leukemia.

Long Term Growth of Diabetic Children. A. E. FISCHER. Am. J. Dis. Child, 64: 413, September 1942.

The growth and development of forty-four diabetic children were studied. They were treated for at least five years, and some as long as fourteen years. Although these children were somewhat overheight at the onset of their diabetes, their rate of growth subsequent to the onset of diabetes was less than normal and after some years they were below average height.

The weights of most of the children were below normal when they were first seen, due to the rapid loss of weight which occurs with the onset of diabetes. This initial weight loss was rapidly restored under treatment. Weight was well controlled by the food intake. Nevertheless there was a tendency for diabetic girls to become obese during puberty and

for boys to become underweight. Greater physical activity on the part of boys may explain this difference during puberty.

Meconium Ileus Associated with Stenosis of the Pancreatic Ducts. E. S. HURWITT AND E. E. ARNHEIM. *Am. J. Dis. Child.* 64: 443, September 1942.

A case of meconium ileus associated with stenosis of the main pancreatic duct and cystic fibrosis of the pancreas is reported; this is the second case in the literature.

A histologic study of the pancreas by serial sections is presented.

Investigation of early embryos reveals that the pancreatic ducts, in contrast with the biliary ducts and the duodenum, do not pass through a stage of occlusion by epithelial proliferation.

The cause of congenital stenosis of the pancreatic ducts is a focal developmental defect.

The basic lesion in meconium ileus is assumed to be interference with the passage of pancreatic enzymes into the duodenum; the practical application of this concept to the therapy of meconium ileus is discussed.

Clubbing and Hypertension Osteoarthropathy. M. MENDLOWITZ. *Medicine*, 21: 269, September 1942.

Symmetrical clubbing of the fingers and toes may be acquired in the course of various systemic diseases or may be hereditary. Unilateral and undigital clubbing apparently occur in association with vascular and vasomotor diseases of the corresponding extremity or finger. Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of the extremities and may develop in any condition capable of producing clubbing.

Characteristic clinical and roentgenological changes occur in clubbing and hypertrophic osteoarthropathy. Clubbing and hypertrophic osteoarthropathy are seen pathologically to consist chiefly of tissue hypertrophy and hyperplasia. In the original bone, however, osteoclasia and bone resorption may be stimulated.

Hypertrophic osteoarthropathy was produced experimentally in the dog by anastomosis of the pulmonary artery to the left auricle. The most significant circulatory change found was an increase in systemic cardiac output.

Clinical physiological observations have demonstrated in simple acquired symmetrical clubbing an increase in blood flow per unit of tissue caused chiefly by an increased digital arterial pressure. In hereditary clubbing and in hypertrophic osteoarthropathy these changes in digital pressure and blood flow were absent. In unilateral clubbing they were variable.

Previous theories on the pathogenesis of clubbing are reviewed historically and discussed critically.

It is believed that increased peripheral blood flow will form a corner-stone of future theories on the mechanism of clubbing and hypertrophic osteoarthropathy.

An Improved Continuous Drip Apparatus with Special Reference to the Use of Alumina Gels in the Therapy of Peptic Ulcer. A. CORNELL, AND F. HOLLANDER. *Rev. Gastroenterol.* 9: 354, September-October 1942.

Difficulties have been commonly experienced in the control of the drip apparatus for the continuous intragastric instillation of antacids in ulcer therapy. In the particular commercial apparatus formerly employed, the authors traced the difficulty to faulty construction of the air-inlet valve in the reservoir flask. The present report describes a modification of this valve which has resulted in the complete elimination of all trouble arising from excessively rapid or complete cessation of flow. The modified apparatus has been used both on hospital and on ambulant patients at home for continuous 24 hour administration of milk-bicarbonate mixture or alumina gel. The vigilance of both nurse and patient which were previously an absolute necessity are no longer required. In fact, the apparatus can be used at home without the aid of a nurse, eliminating otherwise unnecessary hospitaliza-

on. This improved drip is particularly useful for preparations of extremely high viscosity, so great for administration by simple gravity methods, such as aluminum hydroxide gels.

Studies in the Pathogenesis of Experimental Dysentery Intoxication. A. PENNER AND A.I. BERNHEIM. J. Exper. Med. 76: 271, September 1942.

A study of the effects of the intravenous injection of Shiga toxin into dogs indicated that the toxin produces a shock-like circulatory state. A decrease in circulating blood volume is evidenced by a rise in hemoglobin, red blood cell count, hematocrit reading and specific gravity of the whole blood, the specific gravity of the plasma not changing. It was shown that the toxin of *B. shigae* has no direct effect upon the intestinal mucosa when brought to contact therewith, but that its absorption through the mucosa leads to the appearance of a lesion in the duodenum of the dog.

On the basis of these observations and previous work, we interpreted the pathologic alterations in the intestinal tract, following the injection of Shiga toxin, as the anatomic result of a pronounced and prolonged homeostatic vasoconstriction.

Roentgenologic Aid in the Diagnosis of Angioma. J. SCHROFF. J. Am. Dent. A., 29: 1628, September 1942.

Hemangioma of the face and jaw are relatively common and most of them are readily diagnosed by the clinical appearance. Cavernous hemangiomas occasionally form phleboliths which are detected by roentgenograms. Several cases of hemangiomas of face and jaw are cited.

The Roentgenographic Appearance of the Bones in Cushing's Syndrome. M. L. SUSSMAN, AND B. COPLEMAN. Radiology, 39: 288, September 1942.

Osteoporosis occurs frequently in Cushing's syndrome (in 6 of our 7 cases). In the skull, which is most often involved, the changes are irregularly distributed; they are seen most often in the frontal and parietal regions, and are irregularly triangular or ameboid in shape, they may resemble malignant metastases. The osteoporosis in the spine is uniform in degree and extent. The trabeculae are decreased in number and density. The osteoporosis may vary, from case to case, from barely perceptible changes to those of such severity that compression fractures occur in the vertebral bodies. A peculiar change is described in the anterior ends of the lower ribs just lateral to the costochondral junction; the rib is expanded to about twice its normal size for a distance of an inch, and is homogeneously increased in density. These areas cannot be distinguished from callus either roentgenographically or histologically.

By far the greatest number of cases of Cushing's syndrome reported in the literature have an associated basophilic pituitary adenoma. In all of our cases there was a tumor of the adrenal cortex, in some a benign adenoma, and in others a carcinoma.

Study of the Limiting Diaphragm Method of Collimation. S. M. SILVERSTONE AND B. S. WOLF. Radiology, 39: 314, September 1942.

During an investigation of depth dose curves for 200 kv.p. X-radiation, it was found that the method of collimation of the standard equipment being used was defective. By collimation is meant the process of limiting a beam of radiation to a desired size. The defect was manifested by a band of lesser intensity around the periphery of any particular desired field of irradiation. The cause of the defect was traced to the use of a limiting aperture in lead plate placed between the target of the X-ray tube and the end of the cone and usually situated closer to the target than to the end of the cone. The size of this aperture was calculated on the assumption that the radiation originated from a point source. In reality, however, the focal "point" consisted of a rectangular area 1.0 x 1.5 cm. This radiating surface and the aperture produced an umbra and penumbra effect. This explained the lack of uniformity in the field of irradiation.

Collimation equipment of another nation-wide manufacturer showed this same defect.

Defective cones of the above type can be corrected by removing the lead plate containing the limiting aperture and lining the side walls of the cone with lead. The advantages of this type of cone are 1) a homogeneous field of irradiation which remains sharply demarcated to a considerable depth 2) an increased depth dose, and 3) an increased output and uniformity of output with fields of different sizes.

Antipressor and Depressor Effects of Oxidation Products of Pressor Amines. K. A. OSTER. *Nature* 150: 289, September 1942.

The hypothetical sequences of reactions from cyclic amino acids through pressor amines, antipressor and depressor substances to inert end-products are illustrated by a diagram. The equilibrium between these transformations, obtaining under physiological conditions, is disturbed in renal hypertension; the pressor amines then accumulate and at the same time their antagonists are depleted and used up. Extracts with depressor effect have been obtained from normal kidney. In experimental unilateral renal ischemia in dogs the production of the antagonists in the intact kidney prevents the persistence of hypertension in spite of the continuous output of pressor amines from the ischemic kidney.

Salmonella Infection in Infants and Children. S. BORNSTEIN AND H. SCHWARZ. *Am. J. Med. Sc.* 204: 546-550, October 1942.

Salmonella infections in infants and children manifest themselves clinically either as diarrhea under the caption of gastro-enteritis, or as bacteremias with or without localization. The typhoid type occurring in adults and in older children is rather unusual in the first years of life. The stools are usually watery but may be dysenteric in nature. Temperature often accompanies it. However there are cases without temperature and with normal stools which cannot be recognized except by bacteriologic examination. It is urged that all diarrheas in infancy be carefully studied bacteriologically. *Salmonella typhimurium* is the most common type found in human *Salmonella* infection in this country. *Salmonella newport* and *Salmonella montevideo* belong to Group C and show a high degree of invasiveness in man. Agglutination tests are not without value although they are not always positive.

Who Are the Psychiatric 4F's? R. M. BRICKNER. *Ment. Hygiene.* 26: 641, October 1942.

A description is given of some of the psychoneurotic conditions encountered in Selective Service registrants. The reasons why men with such conditions are not acceptable in the armed forces are presented. It is also shown that many of these individuals, while not equipped to stand up under the rigors and limitations of military life, may none the less do very well in the civilian community, to which they have managed to make an adaptation. In fact, they often make important contributions.

The difficulty of succeeding in feigning a psychoneurosis is described. The significance and detection of malingering are discussed, but the methods of detection are not given.

German Philosophy and German Psychological Warfare. W. ELIASBERG. *J. Psychol.* 14: 197, October 1942.

While it is difficult, propaganda creeping into the text, to measure propaganda publications—and also publications on propaganda—on accepted scientific yardsticks, there are nevertheless historical ideas that make for the continuity of the basic policies and the propaganda of a country. The philosophical and psychological background is shown from the German Renaissance philosophy of Leibnitz to Schopenhauer, Richard Wagner, Treitschke, Bernhardt, Nietzsche. The psychology of the Wundt laboratory and later on the applied psychology of William Stern, Ach, Moede and others must be understood against this historical background. The latest phase of German psychology and psychological warfare turns back again to the pessimistic cynicism of mass psychology and on the other hand to an aristocratic propaganda of the key personalities. These two apparently opposite trends in German psychology should be understood by all those who in any way have to

deal with the impact of German propaganda. In final paragraphs the errors of the last phase of German war propaganda in 1918, the phase of the Vaterländischer Unterricht are analyzed; suggestions for the American Armed Forces are developed.

abeas Corpus in Medicine. W. ELIASBERG. New York Physician. 19: October 1942.

Important as the economic and organisational aspects of modern medicine are one should not allow any one to make slight of the personal relationship between the physician and his patient. In a booklet edited under the auspices of the League for Industrial Democracy 1942 the author tells us that a telephone directory listing in bold type is often the deciding factor in the consumers choice of the physician.

Other endeavors symptomatic of the attempt to hamper the personal relationship may be found in group health contracts excluding psychiatric or any other specialist treatments. *abeas corpus* in the medical democracy should not tolerate such encroachments on the physician's and the patient's liberty and happiness.

quinones as Blood Pressure Reducing Agents in Hypertensive Rats. B. FRIEDMAN, S. SOLOWAY, J. L. MARRUS AND B. S. OPPENHEIMER. Proc. Soc. Exper. Biol. & Med. 51: 195, October 1942.

This work is based on the thought that there is a derangement in the metabolism of the amino acids in experimental hypertension (Bing). Holtz originally showed that the first step in the breakdown of l-amino acids is their decarboxylation into amines. This reaction is followed by a deamination of the resulting primary amine to an aldehyde. The first reaction is independent of oxygen, while the second requires oxygen to bring about an oxidative deamination in the presence of amine oxidase. It is possible that in the ischemic kidney the amines formed from decarboxylation of amino acids are not completely oxidized. Since many amines derived from the decarboxylation of amino acids or peptides cause elevation of blood pressure, this mechanism may be used to explain hypertension in animals with ischemic kidneys.

The possibility of bringing about the inactivation of pressor amines *in vivo* through the agency of quinones was tested in the present work. Four or more quinones have been demonstrated to produce marked anti-pressor effects in hypertensive rats, while these same compounds did not significantly reduce the blood pressure of normal non-hypertensive rats. This anti-pressor effect is not associated with any febrile reaction, and it can be elicited by the oral as well as by the parenteral route.

The Classification of Mongolism with the Aid of Capillary Microscopy. C. POTOTZKY. Am. J. Ment. Deficiency. 48: 2, October 1942.

The author tries to make a differentiation of Mongolism cases, especially with the aid of capillary microscopy. After an interpretation of the practical findings of capillary microscopy every single case of Mongolism should be differentiated in the following classifications:

- 1) cases of Mongolism combined with thyroid deficiency;
- 2) cases of Mongolism combined with pituitary deficiency;
- 3) cases of Mongolism with a combination of a deficiency of the thyroid and pituitary glands;
- 4) cases of Mongolism without any apparent glandular combination.

Such an exact classification is important in directing the treatment. Warning is given against treatment of Mongolism at random! Suggestions for other kinds of therapy are made.

Development of Human Eye at Five and Five-Tenths Millimeter Embryonic Stage. A. L. KORNZWEIG. Arch. Ophth. 28: 670, October 1942.

This human embryo measuring five and five-tenths millimeters was obtained from the cavity of the uterus when hysterectomy was done for fibroids. Serial sections of the eye

and semi-diagrammatic clay models were made and described. The development of the human eye at this stage and its blood supply were shown. No eye-lids are present. The lens is still part of the surface ectoderm and is in the process of differentiation. The retina shows only two layers, a nucleated and a fibrous layer instead of the ten layers of the fully developed tissue. No pigment is seen. The blood supply to the retina is by small capillaries as in the brain tissue. In the eye all these capillaries are destined to disappear. The fetal fissure is just beginning to appear and the optic nerve is merely indicated by the short round optic stalk. The eyes are 180° apart practically at opposite sides of the head. Indications of the future development of the different parts were given. Reference was also made to possible congenital abnormalities associated with this stage of eye development.

A New Rectosigmoidal Biopsy Forceps. R. TURELL. *Ann. Surg.* 116: 637, October 1942.

The author devised and described a new rectosigmoidal biopsy forceps. This instrument has a cutting jaw mechanism which operates at an angle of about 30 degrees from the axis of the shaft; the latter has a rotating mechanism which permits 360 degrees rotation of the jaws.

The Efficacy of the Drip Method in the Reduction of Gastric Acidity. A. CORNELL, F. HOLLANDER AND A. WINKELSTEIN. *Am. J. Dig. Dis.* 9: 332, October 1942.

Because of the clinical value of the drip method in treating peptic ulcer, it seemed desirable to compare the neutralizing effects of the colloidal alumina preparations with milk to which a soluble alkali has been added. The investigation was carried out on ambulatory and hospitalized patients, and included studies of the day and night secretion. The acidity (pH) of the specimens was determined by means of the glass electrode. The average pH maintained by the aluminum phosphate and milk-sodium bicarbonate preparations was 4.0 and that of the aluminum hydroxide was 3.5, which is the boundary value for free acid. Thus, all preparations were found to be effective as intragastric neutralizing agent even during prolonged night treatment, when given by the continuous drip method. In the control tests, free acid was absent in only about 1 per cent of the samples; with aluminum hydroxide gel and milk-sodium bicarbonate, this occurred in about 53 per cent and with aluminum phosphate in about 60 per cent. These data indicate that none of these drip procedures succeeded in maintaining the stomach free of acid throughout the entire period of treatment. However, the proportion of high pH values as well as the average pH figures indicate considerable efficiency in acidity reduction.

Effects of Intravenous Injections of L-Dopa upon Blood Pressure. K. A. OSTER AND S. Z. SORKIN. *Proc. Soc. Exper. Biol. & Med.* 51: 67, October 1942.

Peripheral intravenous injection of L-dopa was found to produce a marked rise in blood pressure in cats with experimental hypertension; no rise was produced in cats with acute renal ischemia or in normal cats. Intravenous injection of L-dopa in humans with essential hypertension produced a similar pressor response; a much less marked pressor effect was obtained in humans with normal blood pressure. The possibility is discussed of defective renal deamination due to kidney ischemia as being responsible for the marked pressor response to L-dopa injections in essential human hypertension.

Production of the Schwartzman Phenomenon With A Sulfonamide Conjugate of a Bacterial Filtrate. E. GERBER AND M. GROSS. *Proc. Soc. Exper. Biol. & Med.* 51: 237, November 1942.

A bacterial filtrate of meningococcus known to be capable of producing the Schwartzman phenomenon was coupled with para-aminobenzene sulfonylacetyl-imide. The resulting conjugate was a highly colored substance, easily soluble in alkaline solution. The original bacterial filtrate or the purified conjugate could be used interchangeably as the preparator or the provocative injection for the production of the phenomenon. The chemical treatment of the bacterial filtrate in the synthesis of the conjugate did not effect its ability to produce the Schwartzman phenomenon.

Eye Dominance—Its Nature and Treatment. I. S. WILE. Arch. Ophthal. 28: 780, November 1942.

Vision contains the idea of knowing, and optical acuity does not represent visual habit. Educational inadequacies are medically highly significant as symptoms of organic or functional physiologic disorders and as factors profoundly affecting personality.

The theory of binocular vision and eye dominance is presented. Eye dominance indicates the eye which fixates the object for binocular vision.

Various physical and psychological diagnostic tests are presented and emphasis is placed upon the relations between eyedness and handedness in the learning process. Problems of eye dominance are set forth in terms of total organization of the personality including the level of intelligence and the degree of emotional stability.

The histories of fifty children, victims of dyslexia, studied at the Children's Health Class

The Mount Sinai Hospital, are presented. This group, free from mental deficiency, deafness or optical disturbance, was analyzed in terms of eye dominance and handedness, behavior disorders and confusions in dealing with symbol forms, in terms of educational deficiencies and personality disorders.

The final section deals with the management of eye dominance in terms of re-education of the family and the child. Therapy is outlined in the light of specific re-educational approaches, designed to re-organize the personality and to promote the maximum unilateral eye-hand control in the learning processes.

The Role of Instinct in Human Behavior. J. MARMOR. J. Biol. & Path. Interpersonal Relations: 5: 509, November 1942.

Evidence is quoted from recent advance made in the fields of experimental psychology, sociology, and anthropology which leaves little doubt that the concept of instinct has diminishing scientific validity at each stage of ascent in the evolutionary scale, and least of all when applied to man. A dialectic conception of the inter-relationship between hereditary and environmental factors in the development of so-called "human nature" is presented, and its hopeful implications for the emergence of more integrated personalities under altered cultural conditions is pointed out.

Irregular and Multiple Homonymous Visual Field Defects. I. S. WECHSLER AND M. B. BENDER. Arch. Ophth. 28: 904, November 1942.

The authors report the occurrence of multiple homonymous visual field defects in three cases. The bilaterality and the nature of the scotomas and associated visual symptoms suggested that the lesions were in the calcarine cortex of the occipital lobe. All three patients were comparatively young—39, 42 and 45 years respectively. The lesions apparently were vascular in nature. The patients recovered sufficiently to be discharged from the hospital so that no pathologic reports are available. However, the clinical findings pointed to cortical or subcortical localization. Two patients had visual hallucinations and spatial disorientation. In two cases there was evidence of bilateral involvement. In one of these and in the third, the most likely explanation for the visual disturbance was a vascular lesion in the geniculo-calcarine pathway.

Urinary Phenols. I. Methods of determination. II. Their significance in normal and pathological conditions. M. VOLTERRA. Am. J. Clin. Path. 12: 525, November 1942.

A simple method is described for the determination of three phenolic fractions in the urine, with the Folin and Ciocalteu reaction. The three fractions are: volatile phenols, aromatic hydroxyacids, and nonvolatile, ether insoluble substances, reacting with the Folin and Ciocalteu reagent (residual phenols), which comprise imidazolic constituents as well. The values of these fractions are given for normal subjects.

In normal individuals the elimination of volatile phenols is fairly constant. Food intake does not influence it appreciably. Determinations of the three aromatic fractions in pathologic cases have shown that the intermediate metabolism of proteins is the decisive factor in determining their amount of excretion in the urine.



NEWS AND NOTES

THE ALFRED MEYER ANNIVERSARY VOLUME PRESENTATION

On January 27, 1944, on the occasion of his approaching 90th birthday, Dr. Alfred Meyer was presented with a special number of the Journal of The Mount Sinai Hospital dedicated to him by his colleagues, associates and friends and sponsored by the Associated Alumni of The Mount Sinai Hospital.

Many leading men in medicine, former associates and pupils, as well as many friends and grateful patients came to honor Dr. Meyer.

The meeting was opened by Mr. Waldemar Kops, Acting President of the Hospital. He was followed by Drs. James Alexander Miller and Ira Cohen, who paid tribute to Dr. Alfred Meyer for his highly important contributions in the field of tuberculosis and medicine in general. In his reply, which was replete with interesting reminiscences, Dr. Meyer exhibited his characteristic sparkling wit and good will.

MR. WALDEMAR KOPS:

It is my pleasant duty to welcome you on this occasion when we honor Dr. Alfred Meyer, who has contributed so much, not only to The Mount Sinai Hospital, but to medical science.

Today we are celebrating the ninetieth birthday of our guest of honor, who in spite of having reached an age vouchsafed to few, still retains an insatiable curiosity and a keen interest in the life of the Hospital and in current events. He has never lost the enthusiasm of youth.

Whenever I meet Dr. Meyer I am reminded of a poem written by another eminent doctor. He dedicated a poem to a group of lifelong friends, who although old in years, still were young in spirit. The poet was the famous Dr. Oliver Wendell Holmes and the poem, "The Boys."

I am sure that most of you in this audience are familiar with it, but I should like to recall just a few of its lines, which are indicative of the man we honor,

"Yes, we're boys,—always playing with tongue or with pen,—
And I sometimes have asked,—Shall we ever be men?
Shall we always be youthful, and laughing and gay,
Till the last dear companion drops smiling away?"

So we are gathered today to do honor to a young man celebrating his ninetieth birthday. As Acting President of The Mount Sinai Hospital, and in behalf of its Board of Trustees and Staff, I deem it a privilege and a great pleasure to congratulate Dr. Meyer and to wish him many more years of activity, good health and contentment.

DR. JAMES ALEXANDER MILLER:

It is a great pleasure and privilege to be present upon this occasion celebrating the approaching ninetieth birthday of Dr. Alfred Meyer.

I have known Dr. Meyer for many years and have been closely associated with

him in many activities in which we have been mutually interested. He has always been about two decades ahead of me and when I first met him as a fellow member of the Committee on the Prevention of Tuberculosis of the Charity Organization Society in 1906, I looked upon him at that time as being already one of the elder statesmen, and as a young man I owed much to his inspiring personality and greater experience.

Dr. Meyer began specializing in tuberculosis in 1895. This was at a time when this specialty was not very popular but where the interest of a skilled physician like Dr. Meyer was needed even more greatly than at present.

During the years Dr. Meyer was visiting physician at Bedford Hills Sanatorium, organized the Tuberculosis Clinic at The Mount Sinai Hospital and was one of the great clinical leaders in this field.

He was one of the first to use artificial pneumothorax in this city, a method of treatment which has been one of the greatest advances of modern years.

Dr. Meyer's contribution to the organization of the anti-tuberculosis movement was perhaps even more outstanding. Familiar as he was with the organization of this movement in Europe, he became one of the enthusiasts to advocate the organization of an International Tuberculosis Congress in this country which with his help and that of other leaders of the medical profession, was held in Washington in 1908 and was extraordinarily successful, marking an important milestone in the American anti-tuberculosis movement.

Two of the most important results of this Congress were the emphasis upon the use of exhibits for popular education concerning this disease and secondly the fundamental importance of sanatorium and hospital care for tuberculosis patients rather than having them treated in their homes.

Dr. Meyer was active in following-up both these leads and the very large important tuberculosis exhibit was moved from Washington to New York and was set up in the Museum of Natural History where many thousands attended and the accompanying publicity did much to start the general education of the public as it exists today. Dr. Meyer was particularly active in obtaining the funds to make this possible, which came partly from the city, from the Sage Foundation and from private sources, particularly from Mr. George Blumenthal whose generosity also erected this beautiful auditorium in which we meet today.

Following up the need for more institutions for the care of the tuberculous Dr. Meyer was one of the most active of the physicians who took a leading part in the establishment of the New York State Sanatorium at Ray Brook and later the New York City Sanatorium at Otisville.

During all these years Dr. Meyer was a very active and influential member of the Charity Organization Society Tuberculosis Committee, which was one of the leading organizations for the prevention of tuberculosis in the country at that time. When this Committee was merged into what is now the New York Tuberculosis and Health Association in 1919, Dr. Meyer was one of the charter members of the new Association. In both of these activities my relations with Dr. Meyer were very close and my admiration for his skill and devotion was unbounded.

His personality was characterized by energy, enthusiasm and great kindliness. This latter attribute is evidenced by one incident among many; that is, Dr. Meyer, every year at the time of the Christmas Seal Sale, has made it a point during all the years up to the present time, to visit the office of the Association to inquire as to the progress of the sale and to speak words of kindly interest and encouragement to the members of the staff who have learned to look forward to his visits with much pleasurable anticipation and who always remembered him and speak of him with sincere affection.

These personal attributes account for Dr. Meyer's youthful spirit which belies the calendar of his years.

He has been through his long life a public spirited citizen, always willing to give generously of his time and energy to community service but perhaps above all we will remember him as a kindly, courteous gentleman, sensitive to the feelings of others but subconsciously aware of his own innate dignity.

We, therefore, today honor and respect him in the fullness of his years for what he has done for humanity, for the practice of medicine in his chosen field and for the community as a whole. But most of all we gather here today to pay him a tribute of our deep regard and sincere affection.

Each decade as it is passed in a man's life marks a milestone. Dr. Meyer is approaching such a milestone, the attainment of which is vouchsafed to very few.

Recently I came across a bit of verse on "Growing Old," and if I mistake him not, Dr. Meyer's own sentiments will agree with those expressed by the poet.

"Don't trouble more to celebrate this natal day of mine,
But keep the grasp of fellowship which warms us more than wine.
Let us thank the lavish hand that gives world beauty to our eyes,
And bless the days that saw us young and years that make us wise."

DR. IRA COHEN:

Dr. Meyer, it is twenty years since I addressed you as formally as this. Though it is nearly twenty-five years since you went off active ward duty your interest in the hospital continues as keen as the day you went off. I doubt that any one who receives a copy of the Medical Board minutes reads them with greater interest or scrutinizes them with a more critical eye or more inquisitive attitude. I should know as I have to answer, as well as I can, the various question marks you scatter over the pages. Many a time after you have visited the hospital I am met by some doctor who either knows you or knows of you and to whom you have spoken. He will say to me "Did you see Dr. Meyer? I just left him." On the speaker's face there is an expression of pleasure, the after glow of the chance meeting with you, but this obtains wherever you go.

When you were retired from active ward duty there was no Journal of The Mount Sinai Hospital. After it came into existence special numbers from time to time have been devoted to men who were currently passing from the attending to the consultant stage. More recently there has been an opportunity to catch up with some of the "old timers." Some may have thought that we were playing a dangerous game waiting until your ninetieth year. But I believe

otherwise, I believe that we may have to establish a precedent by dedicating a second volume to you in your hundredth year. I am sure we shall be glad to do it. Until that time on behalf of the Alumni Association, your colleagues, and your friends it is my privilege to present to you this issue of the Journal dedicated to you.

DR. ALFRED MEYER:

May I preface my remarks with a hearty "thank you" to those who have made possible today's issue of the Journal of The Mount Sinai Hospital and these attendant exercises: To the Associated Alumni who sponsored it all; to the indefatigable Dr. Globus, Editor, under whose faithful, skilled guidance the Journal has become an instrument of education in postgraduate medicine; to Dr. Miller, for many years my co-worker in the anti-tuberculosis movement; to Mr. Kops the Vice-President of the Hospital—although we all regret the illness of the President, and wish him a speedy recovery—and to all the sympathetic colleagues, friends and patients who have contributed intellectually and financially. Last, but far from least, my thanks go to Dr. Ira Cohen, President of the Medical Board, for his gracious words in presenting the volume to me, and for the devoted interest which he has taken in the effort.

Some months ago Sir Gerald Campbell, British Minister to the United States, in an address at the New York Academy of Medicine, pleaded for silence on the part of old men. I take it that he meant silence in the field of statecraft and international relations. Knowing him well as I do, I am sure he would not be guilty of such cruelty as to suggest that we old fellows are forbidden the delights of reminiscing. With your permission, that is precisely what I intend to do. I became an interne here sixty-seven years ago. I promptly stole a march on the Board of Directors (as they were known then) by smuggling a piano into my bedroom. With the help of Dr. Davison, my Senior Interne and a splendid violinist, together with a cellist friend from outside, we were soon playing trios. So far as I know there was never a complaint of our "music-making." On the contrary, one morning on rounds, I said to an ex-Union soldier, "Well, Mr. Quarter-master, what kind of a night did you have?" whereupon he replied, "to tell you the truth, Doctor, your music did me more good than your medicine."

In my day the house staff consisted of only four men and there were only two services—Medical and Surgical. Lexington Avenue (I need scarcely remind you that I refer to the old hospital) was unpaved, poorly lighted and unsafe. Across the way, where the Seventh Regiment Armory now stands, was a sunken lot filled with a village of straggling shanties. The nursing was done by scrubbing maids who were taught to take pulse, respiration and temperature and to perform some simple bedside tasks like catheterizations and giving of hypodermics. Of course, they never assisted at operations. There were a few elevators on the premises, but they didn't elevate, because they seldom ran. There was a Dispensary, but it didn't do much dispensing. It was only an embryo, limited to a few small rooms in the basement with primitive equipment and a not-too-punctual medical staff. In their absence we internes were called upon to

substitute, even in the matter of extracting teeth. One detail of the hospital construction was always a mystery to me. How came the architect to put rainscooting in all the wards? Naturally, they were breeding places for roaches and other objectionable creatures. I suppose it was not such a mystery after all, for were not architects entitled to make mistakes due to ignorance the same as the medical men?

During my internship Lister's antiseptic method held sway. All operations were performed in an atmosphere of carbolic acid spray, our clothing was saturated with its odor and I remember when I visited my home, I was always told they could smell my approach several blocks away. There were no laboratories, no medical library, no social service, no bedside teaching, no research and very few autopsies. As to autopsies, how could they be expected, for it was learned sometime later that the officer responsible for getting them used to approach the relatives who had to give their consent, with the query: "You don't want a postmortem, do you?" Small wonder that his efforts were not often crowned with success!

The founding, in the early eighties, of the Montefiore Home for Chronic Invalids, as it was then known, was a godsend to The Mount Sinai Hospital as it freed many beds for the use of acute cases. The minutes of our Board of Trustees refer to a case that remained at the Hospital for six years, but I personally know of a woman patient suffering from a disseminated sclerosis of the nervous system who was with us for twenty years. So far as I know, she held the record and still holds it.

Coming down to more recent times—but not so awfully recent—on the day of the Great Blizzard, Monday, March 12, 1888, I was the only member of the Attending Staff to reach the Hospital. A few years ago I tried in vain to find the registry to see my name in splendid isolation, but quite naturally the Hospital doesn't store the records for fifty-six years!

These are just a few of my recollections of the old Mount Sinai Hospital. Oh, yes, I could give you more! But I will remember Sir Gerald's warning and shall temper my enthusiasm with mercy. Remember, however, that the quaint statements which I have made were not to disparage our beloved institution, on the contrary, it was on a higher plane than many others, but rather to accentuate the marvelous growth and improvements that have taken place. Being a physician myself, I have said nothing of the splendid work of the men who after all have been and are the very soul of the Hospital. An institution for the care and cure of disease can be no greater than its physicians. But I cannot refrain from paying a special tribute to our Board of Trustees which actually aims at even greater achievements. Only a few months ago, they published "Some Studies on the Future of The Mount Sinai Hospital." I inscribed my copy at the time as follows: "Painstaking, thoughtful and stimulating." Under such leadership we can face the coming years—difficult as they may be—with confidence that they will bring increasing glory to our great institution.

MESSAGE FROM THE THIRD GENERAL HOSPITAL

The Third General Hospital, U. S. Army—The Mount Sinai Unit—has now been in North Africa for more than a year. During that time it has established a record in which the Hospital and the Army Medical Corps may take pride.

Preoccupied as they are with the work in hand, the members of the Unit manage to find time to send occasional brief messages to the Hospital which reveal by implication rather than in detail the dramatic story of the Third General Hospital's strenuous activities. From these and other letters addressed to members of their families and friends at home, it is possible to piece together part of the story of the Unit which will probably only be told in full after the war. Some of the highlights are contained in the following excerpts.

The Commanding Officer of the Base Section in which the Third General Hospital is located visited the Hospital in December. He subsequently sent the following official commendation to Col. George H. Donnelly, Commanding Officer of the hospital:

"Following my recent visit and inspection to your hospital, I desire to express to you and to your staff my sincere commendation for the outstandingly efficient administration of your hospital.

"From an administrative standpoint, your hospital appears competently managed and efficiently operated. From a medical viewpoint, all professional services appear to be functioning with unusual smoothness and effectiveness.

"It is felt that your hospital could well be a model for similar institutions and that you have set a standard worthy of emulation."

Col. Donnelly himself has the highest praise for the Unit under his command. In a holiday message to Mount Sinai Colonel Donnelly declared:

"Everyone is doing fine over here. The group as a whole is turning out an outstanding job to make this the best general hospital in North Africa. You may be justly proud of those whom you have sent here."

It was only recently that friends of the Unit at home learned from fragmentary hints that the location of the Third General Hospital was at one time in an active combat zone. In fact, the Unit was close to the shooting, if not in the actual firing line. Casualties from an adjacent airfield were brought directly to the Hospital.

Some of this information first arrived through the medium of a publication issued by the enlisted men of the Third General Hospital. The men called their newspaper "Beach-Head," and in the first issue, in November, they explained why:

"Our activities have led us into pioneering and adventure and instead of the sheltered, composed existence of our original idea of a general hospital, our lives have been fraught with danger, excitement, and a plunge into a combat zone where we truly established a Beach-Head in the activities of the Medical Corps.

"We have assisted as longshoremen in order to 'keep 'em flying', have out engineered the Engineers with our own construction and utility organization, our transportation is as mobile as a panzer outfit; we are supreme in the tent

aching and bivouac field and have served in our present location as one of the largest evacuation hospitals in North Africa in conjunction with our essential functions as a general hospital.

"Under the leadership of our valiant Colonel, we have established a Beach-head in the history of Army Medicine and have planted the Red Cross of the Medical Soldier at the elbows of our fighting brothers, furnishing them, in range of enemy fire, with all the comforts, science and medical aid at the disposal of the United States Army."

A letter from one of the officers of the Unit revealed parenthetically the part the Third General Hospital played in the Sicilian invasion. He wrote:

"Following the hectic period of the Sicilian campaign, where we had practically grand stand seat, there is now relative peace and quiet. We have become so accustomed to running at double over capacity, that functioning like a true general hospital instead of a three ring circus, seems like a terrific comedown. Looking back at our performance, during this present lull, I should say we did a good job. We saved lives, we managed unavoidable hazardous complications following operations well done, further forward. We handled infections and expedited convalescence in cases where the exigencies of warfare had prevented the full use of all the means and talent which are present in the more forward echelons. At the same time we were getting casualties directly from an adjacent airfield. In addition we learned a great deal of future value. We waded into the paper work, staying up all night on occasions, to get the men off on a hospital ship. We have done well and will do better if we get the opportunity."

In striking contrast to these accounts of action was the story of Christmas at the Third General Hospital as related in a letter from Major Ruth Chamberlin, Head Nurse of the Unit. On Christmas Day, Major Chamberlin wrote:

"Last night a group of us went all around the post singing carols for the patients. We carried lighted candles which made the faces very lovely to look at. The nurses wore blue coats and slacks with white shirts. The men wore D. D.'s. All looked well dressed and very happy. The patients who could, came out on the hillside and sang with us. Through the generosity of a neighbor farmer we received a large cypress tree which we placed on top of our hill. The nurses painted forty light bulbs and by begging and stealing we got enough sockets to have a lighted tree. The paint formula might be of interest—Yellow—dissolved atabrine. Green—atabrine and green ink. Red—red ink and talcum powder. The Red Cross gave us a lot of powder paint too, but we especially enjoyed the improvisation. There were services at 10:15 and at midnight for patients and personnel. It was a cheering sight to have the tree for light and color.

"It is now the day after Christmas—Yesterday was a busy but happy day for the patients and so for us. On some of the wards where the beds are down the middle aisle, the beds were covered with clean sheets and turned into one long banquet table. Many of the patients were able to sit at the table where there were gay napkins—designs by 3rd General. You would be amazed to see



As numbered on the picture: 1. Captain Simon Dack; 2. Lt. Thomas K. Ballard, Jr., (MTC); 7. Captain Irving Solomon; 8. Lt. Howard W. Pertulla, (MAC); 9. Lt. Robert S. Day, (MAC); 10. Lt. Robert S. Day, (MAC); 11. Lt. Robert S. Day, (MAC); 12. Lt. Robert S. Day, (MAC); 13. Lt. Robert S. Day, (MAC); 14. Major Solomon Silver; 15. Captain Robert I. Walter; 16. Captain Harold A. Wein A. Weinstein; 21. Captain I. Scotty Schapiro; 22. Major Abou D. Pollack; 23. Captain Vernon I. Allen; 28. Lt. Henry Tavel, (Chaplain); 29. Major Irving Somach; 30. Captain 34. Mr. Norman Greenberg, (WO); 35. Lt. Col. Samuel Karelitz; 36. Lt. Col. Percy Klingenstein; 37. Lt. Col. Percy Klingenstein; 41. Captain Moses H. Holland; 42. Captain Ralph E. Moloshok; 43. Maj Price, (MAC); 48. Major Leon Ginzburg; 49. Captain Morris F. Steinberg; 50. Captain Louis R. E. Zaretski; 55. Major Edward J. Bassen.



1, (DC); 4. Captain Hyman Levy; 5. Captain Henry Doubilet; 6. Major Lester R. Tuchman; 7. Major Abraham Penner; 11. Major Abraham Penner; 12. Captain Gerson J. Lesnick; 13. Lt. James W. Polkinghorne; 18. Lt. Col. Denis D. Glucksman, (DC); 19. Captain Jack Levy; 20. Captain Ed-ward A. Steck, (MAC); 25. Lt. Isidore Zipkin, (SC); 26. Captain Milton Schwartz, (DC); 27. Cap-Edgar M. Bick; 32. Lt. Ralph Peters, (MAC); 33. Captain Henry I. Cohen, (DC); 38. Lt. Nathan M. Zombach, (SC); 39. Captain Lee R. Kulick, (DC); 40. Captain Sid-Edgar M. Bick; 43. Col. George H. Donnelly; 46. Lt. Col. Herman Lande; 47. Lt. Russel W. Polman F. Dunne, (Chaplain); 52. Major Moses Swick; 53. Major Ameil Glass; 54. Major Louis

plain white napkins trimmed with scenes cut from Christmas cards and wrappings. For center places many of the wards had local oranges and fresh dates. The colonel and I visited all the wards. We found each beautifully decorated—some with fire places, all with scenes on the windows and many novel displays. One nurse had walked four miles and bought sleigh bells—horse bells if you are a literalist, and upon return she made a sleigh for gifts for her patients. She paid ten dollars for the bells and with the help of assistants she had obtained enough cigarettes and candy rations so that every man had a gift or two.

"Our Christmas dinner included turkey and a fruit pudding with a very, very tasty sauce. I hope that you all were able to obtain as good a meal. Several of the nurses gave their small candies so that we could have individual nut cup with candies and peanuts for each. The cups have been made for some time by the nurses on our sick ward. We have few sick nurses from our own organization but we care for outsiders who like something to do. The afternoon was festive with more ward parties and a party at the Red Cross. By the way at supper time the "Red Cross girls ("our Quints," there are five) appeared with gift for each of us—candy, cigarettes, cards and a little note book.

"Last night we had a party for ourselves. Our fire place is just finished in the club. It is a sight to warm the soul as well as the body. We had the first music by our own orchestra too. Oh, there comes the red line. So thank again to you all and best wishes that we may be with you in the Old Country next year."

The peaceful interlude apparently did not last very long. The most recent news contains a hint that the Unit is again in the full swing of action. It is reported that the enlisted men have had to discontinue their publication "Beach Heads" because they do not have time for it at present.

STUDIES ON THE FUTURE OF THE MOUNT SINAI HOSPITAL

This study was prepared at the direction of the Trustees of The Mount Sinai Hospital. The attending circumstances are of interest, because they indicate the breadth of vision of the Trustees, and their concern with all matters that may directly or indirectly affect the institution. Last year plans for future growth of the Hospital, which had long been on the agenda, began to mature. In order that, in making decisions, they might be fully conversant with the trends of contemporary thought on the probable lines of development of voluntary hospitals, the Trustees directed the Public Relations Office of the Hospital to draw up a summary of informed opinion on the subject. The results of the survey are embodied in this report.

The Future of the Voluntary Hospital

A SURVEY OF OPINIONS

The past two decades have brought an increasing general interest in the future of the voluntary hospital. This is part of a process which has had a notable development during the same period, of appraisal of the entire field of medical care and public health.

Up to the time of the First World War, the community as a whole concerned itself with questions of medical care only to a limited extent. A number of specific fields were marked out for governmental or philanthropic action—for example, the licensing of medical practitioners, sanitation, and provision of medical care for the poor. Outside of these sectors, the citizen's health was considered his private affair—or a matter between him and his physician.

But during the past generation the subject of medical care has been drawn into the arena of public discussion to an ever-increasing degree. It has become a topic of social agitation and political debate and it has furnished the theme for a multitude of books, articles and speeches aimed at a wide audience. Extensive fact finding investigations have been conducted regarding the availability and need of medical care, among the general surveys being those of the Committee on the Cost of Medical Care, the Julius Rosenwald Fund, and The American Foundation. Lately it has been extensively discussed in the Beveridge Report in England, and the report of the National Resources Planning Board in this country. In all of these discussions the position and prospects of the voluntary hospital have naturally been a topic of prime importance.

This national and international discussion would seem to be of vital importance to the voluntary hospitals, since the attitude of the public and in the long run the future of the hospitals is to a large degree being molded in the debate. Yet in all the mass of literature which has now accumulated on the subject, there is comparatively little that presents the opinion of the voluntary hospitals themselves. An occasional public comment such as the recent address by Arthur A. Ballantine, Vice President of the United Hospital Fund and President of the Greater New York Fund, at the Symposium held by the United Hospital

Fund in March 1943, some publications by the American Hospital Association, the writings of a scant handful of leaders such as the late Dr. S. S. Goldwater, constitute the sum of the public presentation of the voluntary hospitals' viewpoint.

It is no exaggeration to say that the majority of the writers and the bulk of the literature on the subject envision more or less drastic changes in the support, control, organization and operation of voluntary hospitals. Most of those who bear the responsibility for these institutions, and who uphold the centuries-old tradition of medical philanthropy apparently feel so securely entrenched in public esteem and so independent financially that they see no need to enter into debate to justify the major premises on which their institutions are founded and operated.

It would be beside the point to discuss here whether such aloofness is advisable. But it must be noted that in this summary, representing a cross section of publicly expressed opinions as to the future of the voluntary hospitals, the case on their own behalf is perforce not extensively represented.

Prognoses on the voluntary hospital may be classified into the following major subdivisions: sources of financial support; control of policy and administration; services offered by voluntary hospitals; relations with physicians; and relations with patients (including charges for services).

I

FINANCIAL SUPPORT

It is widely asserted that the sources of philanthropic support for hospitals are drying up. Dr. Hugh Cabot of the Mayo Clinic, former Dean of the University of Michigan Medical School, says, for example, in *The Patient's Dilemma* (1940) that the role of charity in defraying the costs of medical care is diminishing because of the contraction of upper bracket incomes and the "weakening of the concept of charity."

Dr. Cabot foresees that in the future the costs will be paid out of taxes and not by charity. He expresses the hope that this change will be gradual so that "the great structures which have contributed so much to the development of medical care will not be mortally wounded."

Michael M. Davis, Chairman of the Committee on Research in Medical Economics, in his book *America Organizes Medicine* (1941) recommends the expansion of Federal and State aid for hospital construction. Professor Barbara M. Armstrong in her work *Insuring the Essentials* (1932), a report on the six-year joint survey by the University of California and Social Service Research, maintains that America is clinging to outworn charity concepts in the field of public welfare, including health care. "Charities which sufficed well enough for the cases of destitution which required assistance in our less sophisticated periods," writes Professor Armstrong, "are expected to cope with the great sickness, invalidity, unemployment, and similar problems produced by the industrialized society of today."

It is conceivable that Professor Armstrong might at present be willing to

modify or at least postpone this death sentence on charity, indited during the depths of the depression. In fact, it is noticeable that many similar judgments by other writers, as to the collapse of philanthropic support of hospitals, were apparently based on conditions during the worst of the depression years. But there are contributions on the subject written within the past year or two which still hold to this view. Dr. Cabot, in fact, says specifically that the depression did not bring about, but only accelerated, the decline in medical philanthropy.

Another line of attack is the widely-heard argument that the whole field of health, including hospital care, should be a governmental service like police protection and education. Typical of this reasoning is the statement of Dr. Miles Atkinson in *Behind the Mask of Medicine* (1941): "Charity hospitals are a feudal survival. . . . Charity as the only means of obtaining a necessary commodity like medical attention is out of date, and rightly so."

Similarly, Professor Henry Sigerist of Johns Hopkins says in *Medicine and Human Welfare* (1941) that "medicine, like education, will ultimately become a public service in every civilized country."

Increasing support of voluntary hospitals by tax funds is also envisioned by many of the physicians whose views were polled by The American Foundation and published in its extensive report, *American Medicine: Expert Testimony Out of Court* (1937). It is notable that while the hundreds of physicians throughout the country whose views were obtained in this survey expressed a great variety of conflicting opinions on most topics, there is little indication in the report of any outspoken opposition to increased support of voluntary hospitals out of tax funds. Perhaps, however, one may assume that there is opposition to increased use of public moneys for this purpose on the part of the many physicians who, the survey reported, believe that adequate medical care is already generally available.

The viewpoint of a Federal health official should be of interest. Harry H. Moore, Public Health Economist of the U. S. Public Health Service, in *American Medicine and the People's Health* (1927), lists among the "next steps" in the development of medical care, the establishment of more hospitals and clinics for people of moderate means, "with State aid when necessary."

The opinion of Waldemar Kaempffert, Science Editor of the New York Times, is also worth noting. Speaking at the United Hospital Fund Symposium in March, 1943, Mr. Kaempffert said: "There is no way of dodging taxation if we are to care for the families that must live in normal times on incomes of less than \$1,000 and even \$2,000 a year. The American Medical Association admits as much." However, unlike most of those who hold this view, he does not consign medical philanthropy to oblivion.

"Does this imply the abolition of the great voluntary hospitals?" Mr. Kaempffert asks. "The Beveridge report makes no such recommendation, nor does our National Resources Planning Board. But we must recognize that treatment in a hospital is no longer a privilege granted by charity, but a right."

One of those who call for maintenance of the tradition of medical philanthropy is Mr. Ballantine, in his address mentioned above. He contends that "to give

up or displace the voluntary hospital would be to deny scope and opportunity in one of the most appealing of all fields to the expression and practice of freely accorded individual benevolence.

"The voluntary hospitals are spontaneous associations for human service freely accorded . . . Only a few can have the same spiritual satisfaction in doing for the vast mechanism of Government that they feel in participating and doing directly for their fellows in distress . . . Who would deny to the individuals on the home front personal participation in the relief of physical suffering, personal part in giving of that relief, or lessen freedom in that field for the forces of religion and brotherhood that live in these voluntary hospitals?"

Dr. Goldwater, in a brief but comprehensive review of the subject published in the magazine *Hospitals* (July, 1942), goes a step further by pointing out hitherto comparatively undeveloped potential source of philanthropic contributions. Concurring in the general view that the traditional type of charitable endowment is diminishing and will continue to decline, Dr. Goldwater goes on:

"Must voluntary hospitals hereafter look to the government alone for capital funds? Some communities will need help, but the majority of communities should not, for *under present tax conditions corporations, without great sacrifice, can give substantial portions of their gross profits to community hospitals* for necessary plant development; their willingness to do so has been significantly revealed in a number of recent hospital drives." (Italics are ours.)

Nevertheless, Dr. Goldwater, too, agrees that hospital expenditures for care of the needy must be met "increasingly, under present and prospective conditions, from taxes." He does not regard this development with apprehension so long as increased support by public funds does not entail government operation or control.

Another point emphasized by Dr. Goldwater, which appears to have been overlooked elsewhere, is the fact that hospital support both under the voluntary system and under a Federally supported program, comes from the same source—the earnings of industry.

"The proffered 'security' of a Federal hospitalization program," he holds "is merely the assurance that industry (management and employees) would under legal compulsion, systematically support the community hospitals which they now support voluntarily and somewhat less systematically. Today each community, in some localities a single industry, determines its own level of hospital service and pays for it; but what it pays for hospital service is applied to hospital service and to nothing else. Under a Federal plan, the level of service would be fixed by a government agency, and all or only part of the proceeds of the supporting tax would be used for hospital purposes, as political expediency might dictate."

Views expressed in the two recent ambitious social planning studies, the Beveridge Plan in Great Britain, and the National Resources Planning Board report in this country, are pertinent.

The American plan relies on large-scale taxation to provide the means for

development of adequate public health services and facilities in every county within the country." Federal appropriations are urged, to aid states and localities in developing a system of regional and local hospitals and health centers, distributing physicians, dentists and nurses in accordance with the need, etc. At the same time, the report envisions "continued support from public and private agencies," but without going into details.

The Beveridge Plan would entail reform and further extension of the compulsory medical insurance system which is now widely in force in Great Britain as in most other European countries. It is, of course, a matter of interest to this country that the authors of this study, on the basis of the British experience with compulsory insurance, and despite the admitted shortcomings of the system as it stands, regard it as sufficiently successful to warrant continuation and expansion. On the other hand, the Beveridge report reveals by implication that a scheme of this kind, merely because it is endowed with the title "compulsory health insurance," is by no means a panacea for all ills.

Summary. There is general agreement that traditional sources of voluntary charitable support for hospitals will continue to contract. It is anticipated that they will be replaced in whole or in part by governmental funds. Whether this will, or should, entail government control is a debated point. A promising new source of voluntary support is corporate giving.

II

CONTROL OF THE VOLUNTARY HOSPITALS

Reasoning from the principle that he who pays the piper calls the tune, it might be expected that those who predict the replacement of philanthropy by taxation as a source of support for hospitals, would also expect their control and administration to pass into the hands of government. Comparatively few, however, say this in so many words. Rather, there is a general concurrence among them that the State will assume an increasing degree of supervision, especially in the coordination of the work of the hospital with that of other institutions and agencies.

The typical pattern which they envision is outlined by Mr. Kaempffert:

"We must weave into one fabric public research laboratories, prepayment group clinics, and hospitals, and put all under competent supervision to maintain the highest standards. Possibly there should be a Secretary of Health at the head of a well-organized department. But that Secretary must not be dominated by the American Medical Association. A Supreme Health Authority, composed of leaders of medicine and selected, subject to Presidential approval, by the great medical schools, hospitals, and research institutions, would be better . . .

"Many small centers must become branches or affiliates of those in the large cities, so that new knowledge will automatically saturate the whole fabric, with everywhere uniform quality of medical practice, teaching and medical research. . . . The voluntary hospitals alone cannot solve the problem of national health.

They should be preserved, but they should also be interwoven into the new pattern of medical care demanded by new social necessities."

Mr. Kaempffert's statement is by no means irreconcilable with the views of the voluntary hospitals themselves, if Mr. Ballantine's opinion may be taken as representative. Mr. Ballantine holds that the voluntary hospital "must demonstrate ability to cooperate in a rounded, over-all program."

"There is a tendency on the part of each voluntary hospital to be a bit too much of a world in itself," he says. "Over-individualization is as much of a danger as over-institutionalism."

He goes on to cite a number of spheres in which he believes New York City hospitals can and should cooperate increasingly. These include uniform accounting systems, a rational scale of charges to patients, extension of the Associated Hospital Service (voluntary insurance) to cover ward care and medical as well as hospitalization charges, and finally, "the rounded physical welfare program for the greatest benefit of the entire community."

"Many of our hospitals were placed and developed in a somewhat haphazard way," says Mr. Ballantine. "Today we look for the ultimate realization of more unified programs. In the modern world isolationism is as truly out for hospitals as it is for states."

The big difference between Mr. Ballantine and Mr. Kaempffert, of course, is that the former wants the hospitals to coordinate their efforts voluntarily, while the latter relies on governmental authority to attain this end. But the point of variance, important as it is, is probably less significant than the fact that they agree that in the future voluntary hospitals will give up a significant part of their individual autonomy, the powers thus relinquished being vested in some outside body, public or quasi-public.

One cannot help wishing that Dr. Goldwater could have been present on the platform with Messrs. Ballantine and Kaempffert to join in the discussion. He had emphatic views on the subject of "remote control" of hospitals.

Speaking with all the authority of his personal experience, he declared:

"To direct the affairs of a hospital intelligently and forcefully, a hospital executive must be on the job, and must have adequate authority; his is emphatically an inside job. Hospital administration becomes increasingly difficult in proportion to the remoteness of the controlling power. . . .

"I learned by experience how little a conscientious commissioner can really know about the proficiency and attitudes of the individuals comprising the medical staffs of a string of government hospitals under central direction; although the 27 hospitals under my management were all located in a single city, I know now that I was blind to many of their faults."

Moreover, Dr. Goldwater held that the voluntary hospitals on the whole have a better record for quality and quantity of service, and for meeting community needs, than government hospitals. In such fields as hospitalization for the tuberculous and the insane, which have been preeminently served by government institutions, he pointed out, the facilities are seriously inadequate and the hospital budgets are starved. Moreover, he added, general hospital care

for the sick poor, although it is an accepted government responsibility, is still provided to a greater extent by charitable and religious institutions than by public hospitals.

"There are communities in which the indigent are being neglected, declares the advocate of a government hospital system; government must, therefore, undertake the administration of all hospitals. As I see it," said Dr. Goldwater, "voluntary community hospitals are to be robbed of their indispensable freedom and the public deprived of invaluable services not because the voluntary hospitals have failed but because the government has failed."

Summary. Voluntary hospitals are expected to forego part of their traditional autonomy, as a contribution toward a well-integrated community health program. There is an issue over the question of whether these powers should be delegated to government or to an authority chosen by the hospitals. In opposition to a universal Federal hospital system, it is argued that the government has not made a good record in hospital operation, and that existing shortcomings are the fault of the government and not of voluntary hospitals.

III

SERVICES OFFERED BY HOSPITALS

The most vexed problem in the whole controversial realm of thinking about hospitals is that of demarcating a boundary where the institution's service should end, and beyond which it may not venture on pain of being accused of infringing on the private practice of physicians, impairing their livelihood, and stifling free enterprise in the medical profession.

From the discussions there emerges one major thesis which does command a great deal of support, though it is very far from being unanimously endorsed. This is the vision of the hospital of the future as the hub of the community's health program. Says Mr. Ballantine:

"For the community health program of the future, the hospital is the very foundation. With the remarkable advances in science and in social living the function of the hospital has vastly expanded. . . . We look forward to the development and expansion of our hospitals for still more intensive and rounded service."

The same idea is advanced in the final report of the Committee on the Costs of Medical Care, in various committee reports of the American Hospital Association, by numerous physicians in The American Foundation survey, and by Dr. Sigerist, Dr. Haven Emerson, and Dr. Kingsley Roberts, to mention only a few outstanding individuals.

"The time has come," says Michael M. Davis, Chairman of the Committee on Medical Economics, "for the hospital to assume the place toward which the combined efforts of many public-spirited physicians and laymen have been developing it for more than a generation. The hospital should be the physical and organizational center through which physicians and the allied professions will supply *all forms of medical service to the community.*" (Italics are ours.)

Among the fields into which the hospital will extend its services, the one most

frequently cited is that of preventive medicine. On this theme Dr. Sigerist writes as follows:

"The prevention of disease must become the goal of every physician. . . . The barriers between preventive and curative medicine must be broken down. . . . The general practitioner will remain the core of the medical profession, but alone left to himself, he is lost and cannot possibly practice scientific medicine. He needs the backing of a health center or hospital and a group of scientists whose help and advice he can seek. Medical practice tomorrow will of necessity be group practice organized around a health center which will have health stations as outposts. . . .

"The people need more than a family physician; they need a family health center where physicians will not wait until a sick man calls on them but from where they will go out into the homes and working places in order to help the people before illness strikes. . . . Whether such a health center should be financed through taxation or compulsory or voluntary insurance is a secondary consideration which will depend on the circumstances."

As Dr. Sigerist has indicated in the passage just quoted, another field which people of his way of thinking expect the hospitals to enter is that of home medical care. On this subject Davis asserts that the work of the general hospital and their out-patient departments is not now sufficiently correlated with the general medical care of the patient or with preventive work for him. He says:

"There are probably a thousand hospitals with out-patient departments which by some broadening of scope and staff, could add home care to their present activities and provide complete medical service, but this cannot be done unless some local physicians, qualified to supply general care but at present excluded from the service organization, are admitted to its privileges; nor *unless the economic relations of physicians are altered so as to avoid intense competition on a financial basis.*"

The passage which we have *italicized* in the foregoing statement obviously presents the nub of the controversy over the extension of hospital services. A very large proportion of the medical profession regards any such proposal as a fatal threat to "free enterprise" in medicine. The American Medical Association is the outstanding champion of the view that free competition among medical men is essential. The extent to which the leadership of the A. M. A. voices the views of physicians as a whole on this subject has, of course, been questioned. But the survey of the American Foundation leaves no doubt that a very large body of medical opinion concurs with the A. M. A.—although there is also a large group which is willing to forego the privilege of free competition.

The Foundation's survey elicited from many physicians statements to the effect that not only is there no need for hospitals to explore new fields of service, but that they have already gone too far. The men feel that the hospitals are now competing unfairly in a number of ways with the doctors—in some cases with the selfsame doctors on whose gratuitous services they depend. Dr. Morris Fishbein summed up the case against pushing of hospital enterprise into new realms with his famous statement that the capable general practitioner and

little black bag can care efficiently for 85% of his patients without consultations or specialists—and presumably without the intrusion of the hospital. This statement has not gone unchallenged. It leads directly to the topic of the future relationship between hospitals and physicians.

Summary. A substantial body of lay and medical opinion foresees the emergence of the hospital as the mainspring of an integrated health program for the community. To function in this capacity, some writers anticipate, the hospital will have to serve in fields which it has not previously entered, such as preventive medicine and home care of the sick. Many physicians oppose this development, as a hindrance to free enterprise and a threat to their livelihoods and independence.

IV

FUTURE RELATIONSHIP WITH PHYSICIANS

Discussion of the future relationship between physicians and hospitals falls into two main categories, scientific and economic. There are those who foresee that the hospital will extend its facilities to an increasing proportion of the medical men of its community—that the principle of the “open” hospital will become universal. There are some who proceed further to the assumption that staff members will receive financial remuneration, or still further, to the idea that the hospital will become the major or sole source of the physician’s income. There is a considerable body of medical men who feel that the hospital must take all, or a much larger part, of the members of the profession under its wing, but who do not by any means anticipate that doctors will then abandon private practice. Moreover, there are many who say that physicians, who now donate their services free to the hospital, should receive compensation in one form or another for at least part of those services, but still with no thought that they will become paid employees or will give up their right to individual enterprise in practice outside the hospital’s walls.

Dr. Goldwater, who was anything but a proponent of economic socialization, warmly advocated, that hospitals open their doors much wider to the medical profession as a whole. In the *Journal of the American Medical Association* (March 28, 1925), he wrote:

“The key to nearly everything that makes for efficient medical practice today is in the hands of the hospitals. Their duty is plain—they must open wide the door of opportunity, so that the entire medical profession may enter in, for the fruits of medical progress belong of right to the many, not to the few.”

Referring to Dr. Fishbein’s “little black bag” statement quoted previously, Michael Davis declares:

“How long can the isolated physician in a large city, practising among people of small means, keep himself up to date, able to do good work for the 85 percent, and decide wisely as to who should constitute the 15 percent for whom special service is needed?”

The answer, he indicates, is that the members of the profession at large must have the opportunities now offered to a minority through hospital affiliation.

A new phrase, "medically indigent," was added to the jargon of social service to describe that large segment of the citizenry which, while financially solvent in other respects, was unable to meet the cost of such an emergency as serious illness. Hospital accommodations and services planned for this group, such as the semi-private room, group nursing, and consultation clinics, have proliferated rapidly in recent years, and it is for them that pre-payment plans such as hospitalization insurance have been designed.

The question was analysed, and some possible solutions indicated, in one of the publications of the Committee on the Costs of Medical Care in 1930. Some of the problems pointed out by the Committee have since been met, or are in process of being met, while others still await action. The Committee's report stated that hospitals were relatively better prepared to serve the two extremes of the economic scale—the well-to-do and the poor—than the middle income group, but that they were ameliorating this situation by modifying their building structure (providing more semi-private rooms, dividing wards into cubicles, etc.) revising their rate schedules, etc.

One of the difficulties pointed out by the Committee was friction between hospitals and physicians as to the sharing of the limited sum available for medical expenditure out of restricted incomes. Another unsolved question, this 1930 study declared, was whether, assuming that every possible device for economy had been adopted and that charges had been equitably distributed, the patient of moderate means could normally pay the cost of his hospital accommodations, his physician, his special nursing, and the "extras," out of his income.

A number of later studies have answered this question—in the negative—for a large part of the middle income group. Some illuminating figures are contained in subsequent publications of the Committee on the Costs of Medical Care. A scientific and statistical calculation for the Committee by Dr. Samuel Bradbury arrived at the estimate that the average American family (numbering 4.1 persons) should spend \$310.00 a year for good health care. And in its report "Medical Care for the American People," the committee gave the following figures on actual expenditures for medical care:

<i>Income Group</i>	<i>Yearly Expenditure</i>
Under \$1200	\$43
\$1200-\$2000	\$61
\$2000-\$3000	\$90
\$3000-\$5000	\$135
\$5000-\$10,000	\$246

Hugh Cabot asserts that the 4 percent of American income spent for medical care is inadequate to provide one-half of the population with good care. Leon Henderson, in a special study for the Committee, reported that medical expenditure is the principal purpose for which small loans are made. Analysis of 161,160 such loans showed 45,595, or 28.3 percent for medical care, Mr. Henderson said, while of 115,689 small loans granted by the National City Bank of New York, 35,864, or 31 percent, were for this purpose.

Many authorities have stated that the inability of large numbers of people to meet the cost of medical care affects the health of the nation adversely. According to William H. Welch, "the health field has woefully inefficient distributive service, as compared with its marvelously effective production service in the laboratories of the world."

Harry Moore, citing the very high rate of preventable disease—38 to 59 percent—found in surveys of large groups of the populace, declares that "medicine remains fundamentally an unorganized professional service . . . fundamentally individualistic. . . . The persistence of unnecessary sickness is apparently due, at least in some measure, to this maladjustment."

Moore goes on to say: "As is asserted time after time in modern medical literature, there has developed a pressing need for scientific medical service for such self-respecting persons as are unwilling to accept the privileges of a free clinic yet have not the means to pay the regular charges for adequate service."

Cabot declares: "No country can afford to be complacent in regard to its offering of medical care while such an enormous gap exists between what modern medicine can offer and what the average man actually receives. . . . At best our charitable institutions have rarely been able to offer good medical care except for severe injury or serious illness. At best, they have had to deal with more patients than their staffs could reasonably serve."

Even *Fortune Magazine* has raised its voice on this topic. In its May, 1941 issue, an article on the United States Public Health Service states: "If, in spite of all medical progress, the United States cannot yet honestly call itself a healthy nation, it is chiefly because medical science and service are often beyond the reach of the common man."

It should not be overlooked that there is a large and important body of opinion that does hold to the view that the nation's supply of medical care is more or less adequate. That appears to be the official position of the A. M. A. leadership. It is also the view of a part of the physicians questioned by The American Foundation. It would certainly appear to be the opinion of those who said that the medical schools should cut down their enrollment in order to reduce cutthroat competition among physicians.

But the overwhelming weight of articulate opinion runs the other way. (*Fortune Magazine*, in an article on the A. M. A. in its November 1938 issue, says: "Between the elders and Dr. Fishbein, the A. M. A. has worked against its own purposes by clinging to ideas that, rightly or wrongly, have been discredited, and it finds itself within hailing distance of its own downfall.")

What plans are offered to overcome the insufficiency, or maldistribution, of medical care? We have already discussed at some length the voluntary prepayment plans for hospitalization, and noted that they are preparing to extend their benefits into the field of payment for physicians' services. Although they have come to the fore only in the past few years, voluntary prepayment plans already embrace a very considerable and steadily-growing number of people.

There are many writers who are not satisfied with this accomplishment, contrasting it with countries with compulsory health insurance, for example, Great Britain where 35 percent of the population, and 86 percent of the working pop-

ulation, is covered. The compulsory insurance plans they advocate generally involve payments by employees, employers, and the government. Professor Armstrong argues that "organized medical charity" is "wasteful" to the extent that it gives free care to persons who with "intelligent medical organization" could be paying for it. She calls the United States "the most backward of important nations in insuring essentials to workers."

Surgeon General Thomas C. Parran says that "it is apparent that the time is not far distant when some system equivalent to the British one will be put into effect in this country."

Compulsory health insurance does not satisfy the thoroughgoing advocate of socialized medicine. They point to grave flaws in operation of the compulsory schemes in countries that have adopted them. Mr. Kaempfert, for instance, said that in Great Britain, under compulsory insurance, the service rendered by the physician "is so hurried and poor that in London the district hospital is beginning to displace him. On the Continent conditions are no better. Compulsory insurance is to be avoided. It does nothing for preventive medicine which must be our mainstay, and it does not distribute scientific medicine."

Mr. Kaempfert's alternative, representing the viewpoint of his school of thought, is the public health center, of which his description was given previously. He does offer the private practitioner of medicine a niche for survival. "Let the well-to-do seek him out, as they do now," he says, "and let them pay high fees for what they regard as personal attention. But the chances are that he will join a group of able colleagues, practice scientific medicine on the Mayo principle, and make as much money, on the average, as he ever did."

The question of how medical service is to be paid for is regarded by some authorities as subordinate to the question of what kind of service is to be given—as exemplified in Dr. Sigerist's views, quoted earlier. Dr. Davis says: "Any plans for organized payment of medical care should also aim toward better organization of services and facilities and greater continuity of care for individuals."

Summary. The pressure on hospitals to expand their services into every field of health care might mean that the members of the community, instead of being occasional patients, would become lifelong clients. Whether this will come about cannot be foreseen now. But hospitals are responding to the need for adapting their service to the requirements and financial ability of persons of moderate means. To this end they are modifying their physical plant, their rate schedules, their nursing system, and notably, are building an extensive system of voluntary prepayment. Many critics hold this to be insufficient, and insist that compulsory health insurance is inevitable, while there are others who believe compulsory insurance has failed where it has been tried, and consider that the future lies with socialized medicine.

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THE WILLIAM HENRY WELCH LECTURES

II. RESTORATION AND PATHOLOGIC REACTIONS OF THE LIVER¹

FRANK C. MANN, M.D.

Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota

The causes and processes of development of many of the pathologic conditions of the liver are so intimately associated with the anatomy and physiology of the organ that it is difficult to differentiate between normal physiologic activities and pathologic reactions. In addition there is a hiatus in knowledge of some of the processes that occur in the organ which transform it from the normal state into the condition found by the pathologist at autopsy. In this lecture I shall review the results of experimental investigations in which the objective was to study some of the anatomic relationships and physiologic processes which might be significant in regard to the development of pathologic conditions of the organ. Briefly the results of our studies indicate that the character of the hepatic circulation, the capacity of the hepatic tissue for restoration and the alteration of hepatic functions owing to the activities of the organ in relation to metabolism, especially in regard to the kind of food ingested, are important factors in the development of the pathologic processes we have studied.

The character of the circulation of the liver is important in the development of pathologic conditions of the organ, not only because through it hepatic tissue is exposed unduly to injury but also because it is the limiting factor in repair of the hepatic tissue after injury. The blood draining the largest area of mucosa in the body passes through the liver before being mixed in the general circulation. The hepatic tissue thus becomes the portal of entry not only of the digestive products of two major foodstuffs but also of toxic substances and injurious agents which may pass the barrier imposed by the greatest surface of the body that is especially adapted for absorption.

A detailed description of the circulation of the liver has been given elsewhere (1) but there are some characteristics that appear to be so important in relation to the development of certain pathologic conditions of the organ that they deserve emphasis. The hepatic circulation has two sources of origin, one venous and the other arterial. The venous supply comprises the larger amount of total blood flow to the organ. It is streamlined, a fact which causes the blood drained from any particular region of the gastro-intestinal tract and associated glands to pass through a rather definite and restricted portion of the organ. Diversion of the venous blood supply so that it does not pass through the liver causes atrophy of the organ but sufficient function remains to maintain life. The arterial supply to the liver is relatively small in relation to the total mass of

¹ Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, New York, April 4, 1944.

hepatic tissue. In general it differs very little from the blood supply to other organs.

Since the liver has two sources of blood supply and both are drained from the organ through common channels, there must be a mixing of the arterial and venous blood somewhere within the organ. Wakim and I (2) found that small components from both the venous and arterial sources entered almost all of the sinusoids of the liver, thus supplying a mixture of blood from the two sources to a majority of the hepatic cells, but small regions of hepatic tissue received blood only from the arterial source and other small regions received blood only from the venous source. It should also be noted that we found that there is a large physiologic reserve of the circulation of the organ.

In view of the fact that the liver serves as a portal of entry for substances that pass through the mucosa of the gastro-intestinal tract and is constantly being exposed to injurious agents, it is not surprising that it should have a great capacity for restoration after injury or a loss of mass of the organ, as after surgical removal or obstruction of the biliary outflow of a portion of the organ. While the processes of restoration after injury differ in certain respects from restoration after partial removal of the organ, they have some fundamental features in common. Furthermore, restoration after partial removal is easier to study than after injury. Accordingly I shall discuss it first.

It has long been known that the remaining mass of the liver is quickly restored after the loss of a portion. The older literature has been reviewed by Fishback (3), who suggested that the idea of regeneration of the liver comes down from antiquity, as shown by the myth concerning Prometheus, whose liver was gnawed on daily by the tormenting vultures at the behest of Jove. At any event the occurrence of restoration after repeated loss of hepatic tissue is true. It is possible in species of animals in which the organ is made up of several almost separate lobes to remove the various lobes successively until only one lobe remains. The total amount of hepatic tissue removed and the amount remaining are usually each greater than the estimated amount the animal possessed before hepatectomy.

The time at which restoration is completed and the total amount of new hepatic tissue formed in normal animals depend upon several factors, as the species of animal and the amount of tissue removed. Fishback (3) found that restoration after a fifth to three-quarters of the liver of the dog had been removed was completed in from six to eight weeks. Higgins and Anderson (4) noted complete restoration to the estimated preoperative amount in the rat, from which 70 per cent of the organ had been removed, at fourteen to twenty-one days. These investigators found that restoration did not take place by uninterrupted continuous growth but was cyclic.

The usual explanation for restoration of an organ after loss of a portion is that it is a response to a physiologic stimulus: a physiologic need for more functioning tissue. Such appears to be true in regard to physiologic compensation of the kidney. Following the removal of one kidney, an appropriate physiologic stimulus will cause the remaining organ to double its weight within one week (5).

The first indication that factors other than physiologic need might be significant in causing restoration of the remaining fragment after partial removal of the liver was found quite accidentally by Magath and me (6). We had been attempting by various means to reduce the hepatic tissue in the dog in order to determine if we could produce the alterations in some of the activities of the organ which were so easy to detect in the dehepatized animal. One of the first methods tried was partial removal of the organ. We found that the animal usually had more hepatic tissue after we had removed all that it was possible to remove surgically than it had normally. We then resorted to the usual procedure for reducing hepatic tissue, diversion of the portal circulation from the liver by anastomosis of the portal vein to the vena cava with occlusion of the former (Eck fistula). The loss of the portal blood causes an atrophy of the liver to about half its normal size. When we removed various lobes of liver in an animal in which an Eck fistula had previously been made, restoration either did not occur or occurred only to a slight extent. Evidently restoration of the liver depended upon the portal blood flow.

If a physiologic need was a primary cause for restoration of the liver, such need should exist in the presence of an Eck fistula as well as in its absence. The possibility remained that the physiologic stimulus for restoration originated in the tissues drained by the portal vein and was in amounts too small to be effective when diluted in the general circulation. Also failure of the Eck fistula liver to be restored might be due to the fact that the tissue in such an organ is not normal. Answers to both these questions were obtained in the following manner. A stoma was made between the portal vein and the vena cava in the same manner as in making an Eck fistula. However, the portal vein was not tied and therefore the portal blood could flow through the liver or into the vena cava, depending upon the relative resistance offered by the two channels. The usual standard amount of hepatic tissue was removed immediately after completion of the stoma. Little restoration occurred and the residual hepatic tissue was normal (7).

We have made several investigations for the purpose of determining if a specific physiologic stimulus is responsible for hepatic restoration. None has been found to date. The results of all our experiments appear to indicate that restoration of the liver after partial removal is dependent upon the flow of portal blood through the organ. It appears that the restoration of hepatic tissue occurs primarily in order to maintain the portal pathways and the restoration of functioning hepatic tissue is secondary.

How is this great increase of mass in the residual fragment of hepatic tissue after partial removal of the liver brought about? The results of several studies have been insufficient to supply a complete picture of the restoration of the liver and the conclusions are contradictory in regard to some questions but several significant facts have been learned.

The results of all the more recent investigations, which were done on the rat, indicate that the increase of mass of the restored liver is owing to increase of size and number of the constituent cells of existing lobules. However, some of the first investigators of the problem concluded that new lobules were formed.

Fishback from the results of his studies on restoration in the dog concluded that the lobules did not hypertrophy but that the old lobules gave rise to new lobules at their periphery by budding. I have attempted to secure data on the question by using swine, the only species of animal available for experimental purposes in which it is known that a definite delineating wall to each lobule exists. I have not been able to remove a portion of the liver in swine successfully because the lobes of the liver of this animal are fused together for too great an extent. The question remains unsettled and the possibility that a difference in species exists must be considered.

Likewise the conclusions of the different investigators are not in agreement in regard to the origin of the new hepatic cells in the restored tissue of the liver. The fact that there is an increase of mitosis of the hepatic cells in existing lobules proves that some of the new cells originate from hepatic cells. On the other hand, almost all the earlier investigators concluded that hepatic cells originated from proliferating bile ducts. This phase of the subject has been reviewed by Fishback (3). Accordingly I shall detail only the results of the more recent investigations.

Brues, Drury and Brues (8) studied the rate of growth of cell mass and number of cells of liver tissue in the process of restoration after partial removal. They determined that while the mass of the liver fragment increased more than 50 per cent during the first twenty-four hours after operation there was very little increase of cell number. During the next twenty-four hours the mass increased about 100 per cent and the number of cells increased more than 60 per cent. This ratio of increase of tissue mass to increase of number of cells continued throughout the period of restoration, with the increase of cells lagging one day behind the increase of tissue mass.

They found that the rate of restoration of hepatic tissue is markedly affected by diet. On high carbohydrate and high protein diets the mass of the liver increased less than on a standard mixed diet but there was very little alteration of the increase of cell number. On a high fat diet the cell increase was markedly diminished. In animals fasted after operation, the mass of the liver increased much less than in fed animals. However, the number of cells increased at approximately the same rate as in the fed animals but was greater than in the animals on a fat diet. Machella, Higgins (9) and I found that there was a correlation between the amount of food ingested and the degree of restoration of the hepatic mass following partial hepatectomy.

Brues and Marble (10) studied mitosis in restoration of the liver. Very few hepatic cells in mitosis were found in the normal liver and no increase was noted during the first twenty-four hours after partial removal but visible premitotic nuclear changes were noted. The number of cells undergoing mitosis increased rapidly during the second twenty-four hours after operation and cells in the process of division were noted throughout the period of restoration, diminishing as the rate of increase of hepatic mass decreased. The cells undergoing mitosis were evenly distributed throughout the liver and throughout the hepatic lobule but varied widely from hour to hour. Amitotic cell division was not seen.

Sulkin (11) studied the nucleus in the normal and restored liver. He found that the nuclei in the restored hepatic tissue cells were definitely larger than in the cells of normal liver. He also noted that there was an increase of frequency and magnitude of polyploidy in the restored liver. Polyploidy occurred most frequently in both normal and restored liver in the region of the central vein, indicating that replacement of the hepatic cells occurred in this region.

The investigations on restoration of hepatic tissue after partial removal of the liver have been mainly concerned with studies of alteration of tissue mass and hepatic cells with but little attention given to the stellate cells and biliary duct system. Very little is known in regard to the latter. Fishback (3) described budding of the bile ducts in the interlobular spaces and the proliferation of the duct system at the same pace as the restoration of the hepatic tissue as a whole. Higgins and Priestley (12) studied restoration of the liver in animals in which the spleen was removed at the same time as the hepatic tissue. They found that restoration of the mass of hepatic tissue occurred with slightly more rapidity in the hepatectomized splenectomized animals than in those in which only hepatic tissue had been removed, although the residual hepatic tissue was approximately the same at the time restoration was completed. They noted a great increase of the number of histiocytes in the residual fragment of the liver in the animals without the spleen as compared with the animals in which the spleen was present. There was a marked infiltration of histiocytes in the portal spaces and foci of these cells along the sinusoids indicating the development of hemopoietic activity in the hepatic fragment in the splenectomized animals.

The hepatic tissue that is restored after partial removal of the organ appears normal within a short period after the process of restoration has ceased and no alterations in any of its functions have been noted. Anderson (13) found that the recently restored hepatic tissue was less susceptible to the action of chloroform than normal hepatic tissue. Likewise Lacquet (14) noted that carbon tetrachloride produced less injury to the recently restored hepatic tissue than to normal hepatic tissue. On the other hand, Love (15) found that the recently restored hepatic tissue was more easily injured by yellow phosphorus than the normal tissue. It should be noted that chloroform and carbon tetrachloride produce a central necrosis of the lobule while the lesion caused by phosphorus is mainly peripheral.

I have discussed the circulation and restoration of the liver somewhat in detail because they appear to be of fundamental importance in the process of development of the experimental cirrhosis that we have studied. Cirrhosis of the liver can be produced experimentally by diverse methods. We have employed several methods for producing cirrhosis in our experimental studies but at this time my discussion will deal only with the lesion produced by one substance, carbon tetrachloride.

Lamson and Wing (16) found that typical cirrhosis of the liver could be produced by the repeated administration of carbon tetrachloride. We have employed this substance in several investigations and have found it very useful in causing a condition of hepatic cirrhosis not unlike the lesion as seen in man.

Moon (17), in an extensive review of experimental cirrhosis in relation to human cirrhosis, concluded that the lesion produced experimentally by carbon tetrachloride met satisfactorily the rigid criteria for cirrhosis of the human liver. However, since there are certain differences in cirrhosis caused by various agents it should be emphasized that my conclusions are based upon the study of the lesion caused by carbon tetrachloride.

We have used dogs and rats in our studies on cirrhosis produced by carbon tetrachloride. The toxic agent was given by stomach tube, by injection into the exteriorized spleen and by inhalation. The last proved to be the method of choice. Various methods for studying the resulting lesions have been used. I wish to emphasize two methods because they are not in common use and because they have been of the greatest value in depicting the alterations occurring during the development of cirrhosis.

In studies on cirrhosis, attention, quite correctly, has been focused upon the alterations in the hepatic cells and the growing bands of connective tissue surrounding the diminishing masses of parenchymatous tissue because these are the two most predominant characteristics of the cirrhotic liver. However, in order to observe the process of development of the lesion we found it advantageous to study also the alterations of the vascular bed and the architectural pattern of the hepatic tissue. The former has been done by Wakim and myself (18) by the use of transillumination of the hepatic circulation and Bollman and I (19) have used the customary methods for depicting the supporting tissue of the hepatic lobule. Our studies have resulted in learning but little that was not previously known concerning the process of development of cirrhosis and justification for their recording resides in the fact that we have observed the development of cirrhosis as a continuous process. Our studies have included a large number of observations of the lesion in all stages of development on different animals at various periods after administration of the hepatotoxin and on the same animal by means of biopsies. The process of development of cirrhosis has been observed from the initial lesion until the capacity for even limited restoration was practically exhausted.

Observations on the intrahepatic circulation show that the initial effect of carbon tetrachloride is to cause a transient vasoconstriction followed by congestion of the sinusoids. The walls of the sinusoids become obliterated in small areas, particularly in the region of the central vein, and small hemorrhages occur. Concomitant with the vascular changes, the hepatic cells adjacent to the injured sinusoids become swollen and vacuolated. The enlarged hepatic cells encroach upon both the sinusoids and the bile canaliculi, causing the former to become smaller and tortuous and the latter to be obstructed. Restoration begins in the region of the lobule where the sinusoids are intact adjacent to the injured regions. Complete restoration may occur following a single injury if the injury has not been too extensive.

When a second injury is given before recovery from the previous injury has occurred, more sinusoids and adjacent hepatic cells are destroyed. The uninjured regions of the lobule are more widely separated than after the first injury

and since the injured regions are unequal, restoration causes decentralization of the central vein and increased irregularity of the sinusoids. Repeated injuries duplicate this process but as the uninjured cells are in widely separated groups, restoration takes place with these clumps of cells as foci within the lobule and the normal lobular pattern can never again be reproduced. Since the injury occurs mainly along the pathways of the portal blood and since the uninjured groups of cells become the foci for restoration, the portal vessels decrease and become very tortuous while the blood supply of the remaining hepatic tissue becomes increasingly arterial. Finally a stage occurs at which very little portal blood can reach the hepatic cells and the process of restoration almost ceases. It would appear that the portal blood is as important in causing restoration of the injured liver as after partial removal of the organ. Restoration of hepatic tissue in cirrhosis due to carbon tetrachloride is self-limited because the stimulus for respiration is progressively destroyed with the hepatic tissue. McIndoe (20), in a study of the circulation by injection mass in portal cirrhosis in man, noted the primary failure of the intrahepatic portal circulation followed by a decrease of the arterial blood supply. He concluded that the condition of hepatic insufficiency in cirrhosis is an expression of vascular deficiency rather than of deficiency of the hepatic cell. DuMais (21) by means of a special injection technic has corroborated McIndoe's results in experimental cirrhosis produced by carbon tetrachloride.

The results of studies on the alterations of the architectural pattern of the hepatic tissue during the process of development of cirrhosis are in agreement with the observation made on the intrahepatic circulation in cirrhosis and serve to emphasize one other phase of the process. Since the small masses of hepatic tissue in cirrhosis are enclosed by capsules of connective tissue it has not infrequently been concluded that the connective tissue bands have proliferated in situ and are limiting factors for regeneration of the parenchymatous tissue. While both of these conclusions may be true in some form of cirrhosis and our observations on experimental cirrhosis due to infection would appear to substantiate them, studies on the architectural pattern of the cirrhotic liver following the administration of carbon tetrachloride show that only a part of the connective tissue developed in situ and that it is only a minor factor in limiting the regeneration of the hepatic tissue.

When the injury to the hepatic tissue has been so extensive that the hepatic lobule is not restored as a whole, restoration begins in isolated groups of uninjured cells scattered throughout the original lobule. The restored masses of hepatic cells, upon cursory examination, seem similar in many respects to small new lobules within the original lobule. However, in the process of restoration the normal architecture of the lobule is completely altered. The central vein and supporting tissues are pushed to the periphery and the trabeculae become tortuous. Each successive injury produces a reduplication of this process and the walls between the growing masses of hepatic cells increase by addition from the supporting tissues of the preceding mass. While some proliferation of connective tissue occurs in the capsules surrounding the parenchymatous masses of hepatic

tissue in cirrhosis due to carbon tetrachloride, the main substance for their information is the increment of supporting tissue from the succeeding regions of hepatic tissue restored. Each injury is followed by restoration accompanied by the pushing of the supporting tissue of the injured region to the periphery. In this manner, the blood vessels and bile ducts of the original hepatic tissue may be dislocated for considerable distances.

Alterations of the hepatic pattern in cirrhosis can readily be observed by marking the stellate cells and noting their disposition during the development of the lesion. Many colloidal substances are quickly engulfed by the stellate cells. When India ink is injected into an animal the liver immediately becomes black owing to the retention of the black particles within the stellate cells. The cells will continue to retain the particles for many months. After a few administrations of carbon tetrachloride all the marked stellate cells are found in the periphery of the restored masses of hepatic tissue. Evidently a complete remaking of all the parenchymatous tissue of the organ has occurred. The healing process in cirrhosis, when it occurs after administration of the exciting agent has been discontinued, has two main histologic characteristics. The circumscribed masses of hepatic cells increase in size and approach very large lobules in appearance and the separating bands of supporting tissue become thinner than before injury. The former change is brought about by an increase of the number of hepatic cells which become arranged into a rough pattern of the normal lobule. The latter change is owing to the pressure produced by the growing mass of hepatic cells and in some instances to an actual absorption.

How about the aftermath; how well does the cirrhotic liver perform the many functions of the organ? It is difficult or impossible to answer this question in regard to specific functions but some general observations can be stated. There are two considerations in regard to whether the cirrhotic liver will maintain sufficient functional capacity to support life: (1) the degree of cirrhosis and (2) the amount of protection from functional stress afforded. The former is obvious and well recognized but the latter may not be fully appreciated.

In general our observations would indicate that the life of an animal suffering from severe cirrhosis is in a more precarious position than that of one that has a less advanced lesion. On the other hand the former animal, if carefully protected from functional stress, will in all probability outlive the latter if unprotected. We have maintained dogs in the laboratory in a seemingly normal condition for more than eight years with a liver so cirrhotic that it was only a small fraction of its normal size. Life of such animals is extremely hazardous and slight functional stresses which can be experienced daily by the normal animal may cause death of the animal that has cirrhosis.

We had concluded from the results of our studies on dogs that had cirrhosis that the progression of the lesion ceased when administration of the hepatotoxin was discontinued and that in some instances even a regression of the lesion might have occurred. Experiments on rats which were killed and examined at various periods after the administration of carbon tetrachloride had been stopped were in

accord with the results on dogs. While we have the results of numerous experiments to substantiate this deduction, a recent study on rats indicates that this conclusion must be modified in some respects. In an investigation made for the purpose of studying the healing and final stages of development of cirrhosis, carbon tetrachloride was administered to a large number of rats until a definite lesion had been produced. Subsequently after various periods the animals were etherized and a small specimen of liver was removed for histologic study. I was surprised to find that while the lesions appeared to regress in a few of the animals and remained stationary in others, exacerbation of the lesion was not infrequently noted. I found that this activation of the lesion was owing to the biopsy, usually as a result of infection of the operative wound, which is so prone to occur in an animal that has cirrhosis. Evidently after the cirrhotic condition has been reduced, slight hepatic injury, not due to the original destructive agent, can cause progression of the lesion.

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NEWER ADVANCES IN OUR KNOWLEDGE OF GASTRITIS

BURRILL B. CROHN, M.D.

[*New York City*]

The concept of gastritis as a pathologic state is not new; it dates back to the histologic studies of Fenwick and of Faber upon cadaverous stomachs beginning apparently years ago. Except for the convincing demonstration of complete atrophy of the gastric mucosa, in association particularly with pernicious anemia, no other clinical connotation could be attributed to the so-called inflammatory changes in the gastric mucosa as seen and studied by Faber.

The "newer knowledge" of gastritis is very recent, a matter of a decade or more and is closely associated with the development and the application to the human stomach of the flexible gastroscope of Schindler. Too much credit cannot be given to those who devised early instruments for viewing the interior of the stomach; the ingenious apparatus with its fifty odd lenses arranged on a flexible axis as devised by Schindler represents, in itself, a crowning achievement. With the zeal and enthusiasm of its creator the instrument has been employed by Schindler and now by innumerable of his students and followers on a plan to discover and to note changes in the mucosa of the stomach, normal, involutinal, inflammatory or pathological.

The scientific world will hence never lack an instrument for the detection of gross pathologic disease in the gastric wall, be it ulcer, carcinoma, sarcoma or inflammatory change. By the use of the instrument the less obvious involutinal and inflammatory mucosal changes have been brought within our view. Naturally with a thesis so recently a subject of discussion, many and varied views have been expressed regarding the significance of such mucosal changes, the opinions ranging from those who pin enthusiastic significance to minor changes of complexion and color and texture to those who tend to skepticism as to the true interpretation of such varying pictures.

In the hands of the master, Schindler (1), and based upon the visual findings of the gastroscope, a whole picture of inflammatory gastritis has been predicated as a disease entity, one which is associated with clinical symptomatology, and one which is a disease of considerable frequency and of serious prognostic import. Superficial, hypertrophic and atrophic gastritis are described as characteristic gastroscopic pictures each with a specific set of associated symptoms related to a particular histologic basis.

In superficial gastritis, which is actually an infiltration of the superficial aspects of the mucosa mainly about the necks of the glands, the mucosa loses its highlights, may be spotted with hemorrhagic areas or even surface erosions, the mucosa being covered with glairy mucus.

In hypertrophic gastritis an infiltration occurs in the depths of the mucosa, in and between the fundi of the gland down to the muscularis mucosa. The mucosa through the gastroscope appears swollen, flabby and velvety, and is divided into polygonal plaques by deepening of the normal crevasses. The

folds are rigid; small wart-like protuberances and gross nodules, even to pseudo polyps, dot the surface of the elevated folds.

In atrophic gastritis the mucosa loses its orange-red color, becomes grey green and thin. The bluish vessels in the submucosa are seen more distinctly through the thinned-out mucosa; small superficial erosions are also visible.

In speaking particularly of the hypertrophic form of gastritis, Schindler (2) in 1936 pronounces the prognosis as extremely poor, the mucosa having little tendency to heal. The disease is serious, hemorrhages occur frequently, the patients suffer more than those with benign ulcer. The x-ray diagnosis is not dependable but a complete set of clinical symptoms is described including mainly pain, distress, relief by food, weakness, loss of appetite and weight, and minimal and gross hemorrhages.

One would hardly think that a disease with such well marked clinical features, of such serious prognostic significance, could have been overlooked by the medical practitioner and his confreres in pathology for so many decades, or at least one would surmise that the occurrence of the disease would be one of extreme rarity. On the contrary, Schindler (3) in 1939 reports gastritis in general as affecting 41.87 per cent of a series of patients examined by gastroscope; the hypertrophic form alone with its hemorrhages and ulcerations affected 172 of a series of 1000 cases examined (17.2 per cent).

E. P. Benedict (4), one of Schindler's most ardent supporters, in 1943 found hypertrophic gastritis to be present in 117 out of 1300 routine gastroscopies an incidence of 9 per cent. The clinical picture is well developed with the presence of gnawing, or burning or aching pain in 74 per cent, relief by food in 81 per cent, night pain in 21 per cent, vomiting in 45 per cent, minimal hemorrhage in 42 per cent, and hematemesis in 27 per cent of all cases. Here is not only a truly formidable series of grave symptoms, but also a disease of extremely frequent incidence.

Further confirmation of the clinical picture of gastritis comes from Rivers and Smith (5) of the Mayo Clinic who described gastritis as simulating peptic ulcer in most of its clinical characteristics, even including melena and hematemesis in 33 per cent of a small series of cases. Here for the first time gastric secretory changes are noted in the nature of increased acidity in 35 per cent and a positive x-ray picture of gastritis in 21 per cent of the cases!

Fitzgibbons and Long (6), competent observers, found chronic non-specific gastritis to be present in 37 per cent of a series of 500 disease cases (compared with Schindler's 41.8 per cent). By contrast, of 31 apparently normal students, 22 showed no gastroscopic abnormalities, 7 increased color, and 2 already evidenced hypertrophic changes. Gold (7) found gastritis affecting 34 out of 50 dyspeptic patients examined at an Army Hospital, an important observation which raises the whole question of total disability as a cause of discharge from active military service.

Such a well marked disease-complex should have a characteristic morbid pathology, with well marked cellular changes occurring as peculiar to the disease and absent in the control cases.

The necessity for establishing what constitutes a "normal mucosa" becomes obvious as a basis for comparison; unfortunately the histologic picture of the so-called normal mucosa in the various successive decades of life has been poorly defined until very recent years because post-mortem digestive changes have vitiated the value of routine autopsy studies. It is becoming increasingly obvious that an absolutely "normal" mucosa without cellular infiltrate occurs only in infancy or in the first one or at most two decades of life (Guiss and Stewart (8)). From then on, with each successive decade, a progressive cellular infiltration with lymphocytes and plasma cells, associated with metaplasia of the mucous cells of the neck and body of the gland is a characteristic finding. Benedict and Mallory (9) studied a control group of cases (specimens obtained by operative resection and by autopsy) to determine the incidence and the degree of the inflammatory infiltration of plasma cells, lymphocytes and eosinophiles which they state is shown by virtually every stomach! The infiltration of plasma cells is graded according to the severity and the depth of invasion. Grades I and II are either scattered foci or superficial infiltrates; Grades III and IV involve a half or the whole of the mucosa. Fifty cases obtained by early autopsy after death and 51 cases obtained by operative resection were studied. In only eight instances was the fundus free of changes; in no instance was the antrum unaffected by inflammatory change. Grades I and II of inflammatory infiltrates affected from 10 to 50 per cent of all mucosae examined, and yet were considered by these authors as within normal limits; Grade III was borderline; IV was regarded as definitely pathological. In the fundus, Grades III and IV represent hypertrophic gastritis which is an exaggeration of the "physiologic gastritis" of normal stomachs. The very term "physiologic gastritis" is an apt one, coined to represent the inflammatory or degenerative or involutional changes of the mucosa normally consistent with the advancing decades of life. Since the incidence of anacidity in the general control group of the population has been shown to increase with each decade of life (10) the idea suggests itself that perhaps these normal involutional or inflammatory histologic changes parallel or stand in causal relationship to the diminishing output of gastric acidity in later years. If a physiologic gastritis is a common if not a normal incident in the adult stomach, what then characterizes the histologic picture of chronic non-specific gastritis? Does the mere difference of degree of infiltration or of metaplasia spell the difference between health and such a symptom complex as pain, vomiting, hemorrhage, weakness, anorexia—a serious disease with a poor prognosis? The mucosal study of specimens removed at operation as employed by us (11) and by Benedict and Mallory (9) has been questioned by Schindler, Necheles and Gold (12) as leading to inaccurate observations due to the use of clamps and ligatures at the site of the operation. Schindler (13) himself studied specimens obtained by resection where the use of clamps was avoided and saw characteristic inflammatory changes of gastritis, hence not due to artefact. Recently Gitlitz and Colp (14) compared biopsy specimens, the one obtained at the beginning of an exploratory laparotomy, the second taken from the final resected specimen of the same individual, and con-

vincingly showed that the technic of operation in itself caused no confusing or inordinate changes in the gastric mucosa. Since biopsy specimens are as yet not obtainable through the flexible gastroscope the study of the resected stomach still constitutes the best check-up of gastroscopic findings.

To what extent are the gastroscopic reports of the presence of gastritis verifiable by characteristic histologic changes? The early attempts in this hospital to prove or disprove such a parallelism led to much confusion and frequent gross discrepancies (11). True, we were rather inexperienced with the use of the instrument and criticism of an amateur status may have some validity. Swalm and Morrison (15) in 1941 obtained through the rigid gastroscope biopsy specimens of cases just observed with the flexible instrument; 52 per cent of the cases showed good correlation; the remainder some marked discrepancies. The series of cases is very small (25 cases) and the technic possibly open to criticism.

A more complete correlation between gastroscopic view and histologic changes was made by Benedict and Mallory (9). They found complete correlation in 54.9 per cent and partial correlation in 33.3 per cent. Six cases (out of 51) showed complete disagreement between gastroscopy and histology. This study thus represents a more than fair corroboration of gastroscopic views by microscopic study. The question still remains why an exaggerated degree of a physiologic process should create such a serious picture of a disease, "superficial" or "hypertrophic gastritis" with all its ominous symptomatology and prognostic severity.

A much more convincing picture, gastroscopically, chemically and histologically can be drawn up for the concept of chronic atrophic gastritis. The clinical picture of this form of involutional or inflammatory degeneration is one of dyspepsia, epigastric discomfort, dull pain and fullness, anorexia, periodicity, even hematemesis (Schindler and Murphy (16) Barnett (17)). The changes in the mucosa are severe and advanced, the gastroscopic picture is so characteristic, and the achylia so frequent that there should be little difficulty in establishing this form of gastritis as an entity. Pathologically complete atrophy of the mucosa (Fenwick (18)) with intestinal type metaplasia, heterotopia, Paneth cells, Russell bodies, and fibrous replacement is easily demonstrated in proper cases. But even these microscopic findings are so consistently present in the mucosa of persons of fairly advanced years in normally good health, even when associated with gastric anacidity, that the question arises when do those degenerative changes constitute a real and active disease associated with pain, nausea, anorexia, etc. and when are they incidental findings of age? Is the gastroscope the determining agent in deciding when an atrophic mucosa is causally related to disease and how accurate is such a differentiation?

Gastroscopically many mistakes are common, mistakes of commission and of omission. Frequently a mucosa is reported as gastroscopically normal and yet histologically is obviously in a far advanced stage of atrophy; and vice versa, a pale greyish mucosa showing blue blood vessels may often prove to be a relatively normal mucosa (Swalm and Morrison (15), Benedict and Mallory

)), Gitlitz and Lerner (19)). Ruffin (20) has raised the point whether the gastroscopist by over inflating the stomach may not reproduce the picture of trophic gastritis as an artefact. By air-pressure studies in dogs with a manometer he could efface folds and simulate an abnormal atrophy.

The anacidity of pernicious anemia is an accepted fact in medical science and is most frequently based upon an atrophic gastric mucosa. The question has been raised as to the true nature of the morphologic change in the mucous membrane of the stomach. In the opinion of Jones (21) the atrophic mucosa seen in pernicious anemia and in many deficiency states is not a true inflammation but is an atrophic degeneration of the secretory structure. In most cases of primary anemia gastric symptoms are entirely absent, a state of affairs which is hardly consistent with the complex of epigastric discomfort, dull pain, fullness, distress after meals, anorexia and diarrhea associated by most gastroscopists with the usual picture of chronic atrophic gastritis.

A question which has recently received much attention is the possible relationship of gastric cancer to a preceding chronic gastritis. Konjetzny (22) in 1913 first described such a probable sequence of events, a viewpoint that Orator (23) soon substantiated. Hurst (24) in the Schorstein Lecture of 1929 again emphasized such a relationship as a positive and probable one, pointing out the long years of anacidity that have frequently preceded the onset of gastric carcinoma and the prognostic gravity of such a sequential occurrence. Rhoads (25) drew attention to the unusual frequency of gastric cancer in instances of arrested pernicious anemia as being out of proportion to the normal occurrence in the control identical group of people in the same age-decades. A most competent group of observers at the Cincinnati General Hospital studied the mucous membrane of resected specimens of gastric carcinoma (26). They found atrophic gastritis to be present in 28 out of 35 such specimens of gastric cancer, a figure which compares with Schindler's findings of gastritis, usually atrophic in 33 out of 49 carcinoma specimens. In the Cincinnati group seven cases of gastric cancer failed to show gastritis by either gastroscopy or by histologic study. They later state that they found atrophic gastritis to be present in 36 out of 40 cases of previous peptic ulcer, a percentage which is practically identical with that found in gastric carcinoma. Most of the time the atrophic gastritis could not be seen by the gastroscope or else it was hidden by a superficial gastritis.

This finding agrees with that of Stout (27) who is willing to testify that he was unable to predict the microscopic state of the mucosa from either the gastroscopic appearance or the postoperative gross aspect of the gastric mucosa. Guiss and Stuart (8) confuse the issue still further by demonstrating atrophic gastritis to be present in almost 100 per cent of persons with gastric cancer, but also in about the same percentage in persons with non-carcinomatous gastric lesions in the later decades of life. Yet a recent case in my own experience bade me keep an open mind for the possible sequence of gastritis and carcinoma in the same patient. Five years of subjective symptoms of pain and distress suggested peptic ulcer in a man 45 years of age. A fractional test meal showed a complete achylia gastrica, histamine-proof. Gastroscopy revealed a superficial ulcer with

a necrotic base but apparently an otherwise normal appearing mucosa. The resected specimen showed a marked atrophic gastritis with advanced metaplasia and intestinal-type replacement epithelium (fig. 1). In the area of the necrotic superficial ulceration, a cellular degeneration in the form of a carcinoma *in situ* was histologically verified (fig. 2). Here the sequence of events might lead one to deduce long-standing gastric atrophy, anacidity, gastritis, carcinoma. But as pointed out by Dr. Paul Klemperer, the same incidence of atrophic gastritis might have been found in a very high percentage of so-called normal mucosae in the identical age-group, and in the mucosa of ulcer or of other non-gastric pathologic states so that conclusions founded upon an individual case even though that case seems to fulfil all the postulates, must still remain guarded.



FIG. 1. Atrophic gastritis of long-standing. Disappearance of normal gland architecture. Intestinal metaplasia.

Antral Gastritis: Having shown by citations from the newer literature that the whole picture of "gastroscopic" gastritis and its related clinical symptomology is confused by the varying states and conditions of the so-called normal mucosa in control series as observed by decades of life; having demonstrated many of the inconsistencies between gastroscopy and histologic attempts at verification; having reviewed the inconsistent radiologic and secretory findings in gastritis there still remains one clinical and pathologic condition which is recognizable in its existence, and in its constant clinical picture, namely that of so-called "antral gastritis." Konjetzny (28), Henning (29), Eusterman (30), Benedict (31), and Golden (32) have recognized and described the clinical, pathologic and radiologic characteristics of this entity. Our own experience in

This hospital originally published in 1939 (11) and based upon nine typical cases has been greatly enlarged by an ever-widening experience with a disease which is anything but uncommon. The entity is marked by a diffuse hypertrophic and atrophic gastritis involving one or all the coats of the antrum and pylorus, a gastritis which is uniformly present in all cases. The mucosa is thickened and hyperplastic, usually visible by gastroscopy; pseudo-polyps and even real polypoid formations arising from the mucosa are not uncommon. The submucosa is often enormously thickened to resemble a Linitis plastica, the muscularis propria may be several times its normal thickness and may resemble the benign hypertrophic pyloric stenosis described by Boas (33), by Konjetzny (28) and by Kirklin and Harris (34). The symptoms of antral gastritis resemble those of benign

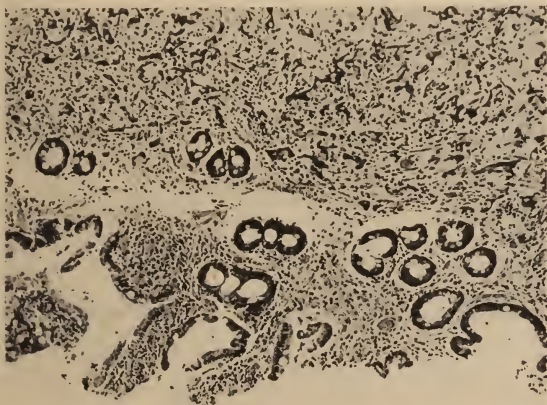


FIG. 2. Carcinoma *in situ*, apparently on the basis of long-standing atrophic gastritis

ulcer or of beginning carcinoma invading the distal segment of the organ. Pain and heartburn resemble ulcer. Loss of weight, anorexia, vomiting suggest carcinoma; periodicity is usually lacking. The course is progressive and continuous and the general loss of weight and of strength is more significant. High acid secretory curves usually dominate in the ulcer-like syndrome; anacidity may be present in the carcinoma-like cases. The gastropic picture is quite characteristic and consists of marked congestion, edema of the mucosa, highlighting, polypoid excrescences. At times such areas of superficial or hypertrophic gastritis are interspersed with areas of atrophic degeneration or inflammation.

Radiography reveals a persistent antral defect, simulating the spastic defect of an ulcer *in situ*, or that of an infiltrating tumor. A true differentiation of the specific underlying factor cannot be made. In the cases resembling neoplasm

anacidity is the rule; occult blood in the feces and even true hematemesis and melena not infrequently occur.

Before the introduction of the invaluable gastroscope only an exploratory laparotomy sufficed to demonstrate the true nature of the apparent defect. Today the typical appearance of the lesion during gastroscopy has revealed those cases that are truly localized inflammations, and have reserved resection for those cases in which the benign or malignant nature of the process cannot be differentiated beyond a shadow of doubt.

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ESSAYS ON THE BIOLOGY OF DISEASE¹

ELI MOSCHCOWITZ, M.D.

CHAPTER 5

THE BIOLOGY OF GLOMERULONEPHRITIS

Between its beginnings and ends, glomerulonephritis may be converted into many clinical syndromes. Some of these syndromes have received different connotations in the past, with the implication that they represent distinct disease species, whereas, in fact, they are merely transitional states. The reason mutation occurs in one or the other direction is not known, although our knowledge of the pathogenesis of glomerulonephritis is fairly clear. To appreciate the biology of glomerulonephritis, it is essential to observe cases from the beginning to the end. Unfortunately, this opportunity is not always at our command and in hospital practice, especially, one is usually in the position to observe only the middle or terminal phases of the disease. Exceptionally, one may laboriously reconstruct the earlier clinical phases. The following observations are based upon a study of a considerable number of cases from the initial to the terminal stage.

Etiology. There is a distinct relation between infection by the streptococcus and glomerulonephritis. The most common focus of invasion is the throat; less commonly, the attack follows scarlet fever. These account for about nine-tenths of glomerulonephritides. In the remainder, are those following streptococcus pneumonia or skin infections. Some cases of "war" nephritis have also been shown to be glomerulonephritides. While the relation of the streptococcus to glomerulonephritis is close, we are by no means clear as to the mechanism whereby this organism causes these lesions; aside from the embolic glomerulonephritides of subacute bacterial endocarditis (a lesion quite different in its morbid anatomy) the streptococcus has never been found in such kidneys. Moreover, these lesions have never been satisfactorily produced experimentally by the streptococcus or any of its known toxins. In all likelihood, the explanation lies in the experimental work of Masugi (1) who produced what appears to be typical anatomical and clinical glomerulonephritis by the injection of kidney antibodies. This suggests strongly that sensitization and the development of resistance to the streptococcus is in some way related to the pathogenesis of human glomerulonephritis. This helps to explain why the glomerulonephritis does not arise at the

¹ This is the fifth in a series of essays by Dr. Eli Moscheowitz in which an attempt is made to interpret certain forms of chronic disease from the biologic viewpoint as opposed to the current trend toward rigid classification implying a concept of disease as a more or less static phenomenon.

According to present plans these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed in the form of a monograph.—Ed.

height of the infection but only when it is subsiding, but it does not explain why the lesion is often progressive despite the disappearance or removal of the "focus."

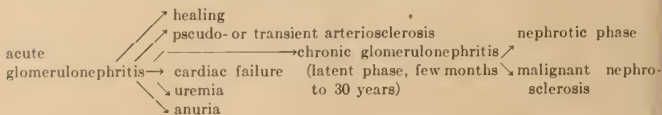
There is reason for believing that glomerulonephritis merely represents the localized expression of a general capillary disease.

Pathology. The earliest lesion is represented by a diffuse swelling of the intra- and extra-capillary endothelium of the glomerular tufts, so that the glomerulus appears bloodless and seems to distend the capsule of Bowman. These cells soon proliferate, especially those lining the margins of the capsule, resulting in the formation of crescents. Young fibroblasts appear throughout the parenchyma, particularly in the neighborhood of the glomerulus. Grossly, in this stage, the kidney is large and white. The subsequent changes in the kidney depend upon the growth and senescence of the newly formed connective tissue. Thus we find fibrosis both within and without the capsules of Bowman, with progressive circumferential shrinking of the glomerular tufts to eventual disappearance, so that the glomerulus becomes converted into a mass of newly formed connective tissue. There is also progressive thickening and fibrosis of the intertubular connective tissue, with resulting deformity, obliteration or dilatation (compensatory) of the tubules. In this stage, the surface of the kidney is finely or coarsely granular, the capsule is adherent and the kidney is somewhat shrunken, the degree depending upon the age of the lesion. If the process continues, further maturation of all these elements results in almost complete obliteration of the normal morphology, the contraction becomes extreme, and there results the secondary contracted kidney which may be red due to the congestion resulting from an associated cardiac complication. Coincidentally changes in the larger blood vessels occur. These have been studied by Fishberg (2) and consist in proliferation of the intima and elastica, in a notable hypertrophy of the muscular coats of the arteries, and, if hypertension is extreme as in the so-called malignant hypertension, in necroses of the vessel wall; in other words, arteriosclerosis is produced, not only within the kidney but in the arteries of the greater circulation. The arteriosclerosis, it may be added, is not the direct result of the inflammatory process but is due to the superimposed hypertension.

In every stage, profound changes in the tubular epithelium occur in the form of fatty and hyaline degeneration or cloudy swelling.

It is important to recognize that the victim may die in any stage of this pathogenesis, even in the earliest. Furthermore, it is impossible to predict the pathologic findings from the clinical data, except in only an approximate fashion. By and large, the longer the duration as disclosed by the history, the more advanced the lesions.

The Biology of Glomerulonephritis



Clinical Evolution of Glomerulonephritis: 1) *Normal course of acute glomerulonephritis.* The disease occurs in young individuals as a rule and usually two to four weeks after the onset of the infection; the first symptom is proteinuria with hematuria and many coarsely granular and blood casts. Puffiness of the face or extremities occurs early, suggesting generalized capillary disease with increased permeability; the blood pressure rises, rarely to untoward heights. There is usually some azotemia which is rarely marked, and headache. If the diastolic pressure rises to 120 mm. Hg. or higher, hemorrhages or exudates appear in the retina. Occasionally, hypertension of the cerebrospinal circuit arises with marked cephalalgia, disorientation, twitching, convulsions, increased reflexes and occasionally papilledema. This complication, however, is uncommon. I have also seen death occur with complete anuria and marked azotemia, with only a moderate grade of hypertension. Usually, improvement ensues within a few weeks after the onset. The subjective evidences disappear, the azotemia returns to normal, the puffiness and hematuria and hypertension subside. The proteinuria persists the longest, sometimes for weeks or months after all other evidences of nephritis have gone. With the subsidence of the hypertension, the eyegrounds return to normal.

The prognosis cannot be gauged by the severity of the signs or symptoms. I have witnessed severe cases get well and mild cases pass into the chronic phase. As a general rule if the proteinuria persists for three months, the probability is strong that the disease will become chronic. In only one instance, have I seen recovery after a six months persistence of the proteinuria.

Death in the early stages is more likely to occur from left myocardial failure than from uremia. Apparently the myocardium is not adjusted to the sudden onset of hypertension even when the pressure is not excessive and therefore fails if an undue strain, particularly an excessive ingestion of fluid, is placed upon it.

2) *The syndrome of pseudo or transient arteriosclerosis.* Some years ago, I (3) reported eight such cases with one autopsy. Since then I have seen many more so that it is not uncommon. It is best observed in young individuals in the earlier stages of the nephritis. The radial arteries feel decidedly thickened. As a rule, the diagnosis is made of an "acute nephritis superimposed upon a chronic one." Curiously, as the patient improves and the hypertension subsides, the feel of thickening disappears, but not when the tension returns to normal, but two to four weeks later. This feeling of thickening is therefore not due to the increased intravascular tension alone, but to the disappearance of the hypertrophy of the muscular layers of the vessel wall, a lesion which Fishberg (2) has emphasized is compensatory to the hypertension, comparable in mechanism to the hypertrophy of the left ventricle. As Fischer and Schlayer (4) demonstrated, the sensation of thickening which an arteriosclerotic vessel affords is due more to the hypertrophy of the muscularis than to the changes in the other coats of the vessel. In the case which ended fatally, no arteriosclerosis of the aorta was demonstrable. The remainder recovered completely.

3) *The latent or proteinuric phase of glomerulonephritis terminating in malignant nephrosclerosis.* This is an exceedingly common sequence of acute glomerulonephritis. We refer to patients who have lost every sign and symptom, including

hypertension, and the only remaining evidence of renal disturbance is a persistent proteinuria, usually of moderate grade. These are the patients so frequently encountered in practice who are rejected by insurance companies. It can be easily distinguished from orthostatic albuminuria because in glomerulonephritis there is always morning proteinuria. Unless one has observed such transitions, these cases may be difficult to interpret, especially when hypertension is lacking. We are so accustomed to thinking of hypertension being a part and parcel of clinical glomerulonephritis that it is difficult to believe that this disease may exist without an elevated pressure in some portion of its biological course.

This latent period of glomerulonephritis may last for months or even many years. I published (5) a case of proved glomerulonephritis which began 32 years previously. Unless cut down by intercurrent disease the patient slowly develops signs of renal insufficiency. The kidney loses its power of concentration, azotemia arises, hypertension develops with resulting cardiac manifestations and eye-ground changes, and ultimately, the patient dies with all the evidences of so-called malignant nephrosclerosis. At autopsy, necroses of the vascular wall are nearly always found, undistinguishable from those witnessed in the malignant nephrosclerosis arising from "essential" hypertension.

Some hold that an acute glomerulonephritis may completely heal without a clinical vestige remaining and may relight in later years resulting in the clinical manifestations of hypertensive disease. Such a sequence is particularly plausible when there is a history of scarlet fever or some other streptococcus infection in childhood. In every such instance that I have observed, the kidneys at autopsy revealed the nephrosclerosis associated with essential hypertension and not a glomerulonephritis. In my experience, once an acute glomerulonephritis heals completely, it remains so, and when it becomes chronic there is always a clinical continuity from the acute stage. And here a distinction must be made between clinical and anatomical healing. Clinical healing does not necessarily imply a complete anatomical *restitutio ad integrum*. Being a productive inflammation, it is difficult to conceive that such a kidney can be restored to its previous integrity, but the anatomical appearance of such an organ, when clinical healing has occurred, is still unknown. It is difficult to find such kidneys because a number of checks are necessary. There must be proof 1) that a true glomerulonephritis occurred in the past 2) that clinical healing occurred and 3) the patient died without any evidence of renal involvement.

4) *The nephrotic phase of glomerulonephritis.* This evolution of acute glomerulonephritis will be discussed more fully in the chapter on "nephrosis." All we need say at present is that it occurs only when sufficient protein is lost by way of the urine to provoke a hypoproteinemia.

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MASSIVE PULMONARY EMBOLISM. II¹

BASED IN PART ON A STUDY OF EIGHTY-EIGHT FATAL CASES²

HAROLD NEUHOF, M.D., AND SAMUEL H. KLEIN, MAJOR, M.C., A.U.S.³

I. ETIOLOGY (*continued*)

F. Venous Thrombosis and Pulmonary Embolism. The prime requisite for the production of pulmonary embolism is, of course, the thrombosis from which the embolus originates.

The pathogenesis of thrombosis is obscure. In general, three main etiologic factors are considered to play a rôle (Aschoff (25, 26, 28), Barker (23), Ewald (21), Belt (7, 24), Cohnheim (30), Wright (96), Frykholm (29), Homans (27), and others). These are:

1. *Factors which alter the wall of the vein.* According to Cohnheim (30), blood will remain fluid in the vessels as long as the intimal endothelium is intact and performs its functions normally. Intimal damage may occur as the result of factors operating from within the lumen of the vessel or from outside the vessel wall. Stagnation of the blood causes intimal injury because it interferes with the nutrition of the vessel wall (Cohnheim (30), Frykholm (29)). Mechanical pressure upon the vessel also contributes to ischemia, with resultant intimal injury. Influences acting from outside the vein include mechanical or chemical trauma and infection. According to Homans (27) the nonsuppurative idiopathic reaction which occurs about the vessels in some cases may be due to a deep perivascular lymphangiitis.

2. *Factors which alter the nature of the blood.* Physical and chemical changes in the blood may be induced by dehydration resulting from limited fluid intake, vomiting, diarrhea, sweating or hemorrhage. Dawbarn, Earlan and Evans (31) have shown that after operations, after delivery (especially Caesarian section), after fractures and during convalescence (e.g., from acute lobar pneumonia) there occurs an increase in the blood platelets during the periods when thrombosis and embolism are most likely to occur. Hueck (32) also noted a similar postoperative thrombocythemia. On the other hand, Potts and Pearl (33) have reported a 6 per cent drop in the average blood platelet count on the first to the third postoperative days following major surgical procedures, followed by a slow rise to 9 per cent above the preoperative level on the tenth day following operation. The preoperative and the postoperative coagulation time of serum

¹ This is the second installment of a series of articles dealing with the problems of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting the second in the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

² From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital, New York.

³ Major Klein, adjunct surgeon to The Mount Sinai Hospital and now serving overseas with The Mount Sinai Hospital Unit, has contributed the study of the fatal cases and the analysis on which the work is based.

and of whole blood remained practically constant with the exception of a very slight drop in the first postoperative day. In view of the average minimal variations in platelet count and coagulation time in patients who have undergone major surgical procedures, the authors were doubtful whether these factors in themselves were of any significance in the development of postoperative thrombosis or embolism.

Aschoff (26) points out that the agglutinability of the blood platelets themselves, in addition to an increase in their number and retardation of the blood stream, is a necessary condition for spontaneous thrombosis. He states that the increase in the platelets following operation or delivery may possibly be a reaction following loss of blood and also remarks that cachectic states cause variations in the number of platelets. Bancroft and his co-workers (34) have determined a plasma-clotting index based on the prothrombin content of the blood. In a series of 920 cases, 111 (12 per cent) showed a high clotting index. Among 54 per cent of the latter who were untreated by the authors' method of intravenous sodium thiosulphate and a high carbohydrate, low protein and low fat diet, there were 9 thrombo-embolic accidents. There were no accidents among the remaining 46 per cent who were treated. Homans (27) has suggested that a product of disuse atrophy of the leg muscles may enter the blood stream and lead to thrombosis. Dawbarn et al. (31) also postulated an absorption of decomposition products of tissue injury.

3. *Factors which retard the circulation.* Virchow (35) was one of the first to point out that slowing of the blood stream plays a considerable part in blood coagulation. Venous retardation may occur as the result of local and general causes. These factors consist of bed rest immobility (due to pain, debility or narcosis), tight bandages, dressings and binders, abdominal distention, pressure of the pregnant uterus or of large intra-abdominal tumors, restriction of thoracic and abdominal respiratory movements, and varicose veins. Eddies and cross currents in the blood stream also contribute to the conditions favorable for the processes of spontaneous thrombosis (Aschoff (26)). The well-known tendency to thrombosis of certain veins may be explained on anatomical peculiarities. For example, as noted by Aschoff, the femoral vein just where the large valves are present lies close to Poupart's ligament, bringing about a bend in the vessel at this point. The iliac vein, shortly after the junction of the hypogastric, also comes into the same category, and its tendency to thrombosis is to be referred to the bend in the path in which the blood flows. With the patient lying on his back, the increased compression of the left iliac vein by the arterial trunks (right iliac, middle sacral, and left hypogastric arteries) has a direct influence in slowing the blood stream and explains the well-known frequency of thrombosis in the left lower extremity. This author brings out still another point. When bilateral thrombosis of the veins of the lower limb occurs, the thrombus on the right side characteristically extends up to Poupart's ligament, whereas that on the left side extends up to the point of compression of the left iliac vein by the right iliac artery. Further evidence suggesting that eddy currents may arise in the femoral vein has been brought forward by Frimman-Dahl (36), who,

by means of venography, visualized retrograde flow from the femoral into the saphenous vein.

Finally, Aschoff states that these local factors play an even greater part when impaired heart action leads to a general slowing of circulation in the venous system.

It has been demonstrated clinically that slowing of the circulation occurs post-operatively. Smith and Allen (37, 38) determined the average foot-to-carotid circulation time in a group of postoperative patients. During the first two days there was at first a definite decrease in the circulation time. However, the average foot-to-carotid circulation time two days after operation was greater than the preoperative average. Beginning about the fifth day, the average foot-to-carotid circulation time increased gradually to a value which at the tenth day was approximately 50 per cent greater than the preoperative average. Eighty-two per cent of individual cases showed increases of circulation time at some time after operation. The arm-to-carotid circulation time, however, changed very little after operation except for decreases shortly after operation. This fits in with the well-known clinical assumption that thrombophlebitis occurs post-operatively in the lower extremities and pelvis.

Frimman-Dahl (36) demonstrated venographically a marked retardation of venous blood flow after operations in which pulmonary embolism is thought to occur most commonly. It was noted that in some cases the rate of flow in the veins was so slow that the blood almost came to a standstill. The retardation was most marked from the second postoperative day and had a tendency to last during the entire time the patient remained in bed. This author also noted that in non-operated patients, the blood flow was retarded during confinement to bed, with the exception of patients suffering from thyrotoxicosis. In two cases in which the venous blood flowed slowly, the formation of thrombus was observed. In other cases, however, in which the flow of venous blood was also slowed, no thrombosis was found.

Further evidence of the importance of slowed blood flow in the etiology of thrombosis and embolism is presented by Belt (7). In a series of 567 autopsies, there were 83 cases of congestive heart failure. In the latter group Belt found 36 instances of venous thrombosis. Twenty-five of these cases had pulmonary emboli and 11 had thrombi capable of giving rise to pulmonary emboli (7 had thrombosis of leg or pelvic veins and 4 had mural thrombi of the right auricle). Forty-nine out of a series of 56 autopsied cases of pulmonary embolism had impaired cardiac function. In correlating the relationship of cardiac incompetence to the development of venous thrombosis, according to Belt, the general assumption is that the factor involved is slowing of the circulation. That circulatory retardation occurs in cardiac decompensation has been demonstrated by the work of Blumgart and Weiss (39). They showed that the circulation time is appreciably prolonged in cases of cardiac insufficiency, that the velocity of flow from the peripheral veins to the right heart is definitely slower than in normal individuals, and that the venous pressure is increased.

The fact that the veins of the leg are the commonest sites of thrombosis leads

Belt to believe that slowing of the circulation is an important factor in the development of thrombosis.

In summary it should be stated that the exact cause of spontaneous venous thrombosis is as yet not known. It is difficult to evaluate the various etiologic factors discussed. However, it seems probable that thrombosis is the result of more than one of these factors, operating in conjunction with one another.

G. Source of the Embolus. In many cases it is difficult or even impossible to determine, either clinically or at limited post-mortem examinations, the location of the thrombosis from which the pulmonary embolus originated. Authors believe the parent site of the thrombus may be missed at necropsy because of incomplete autopsy or because the clot migrated in its entirety, leaving no trace behind.

It was generally thought until very recently that the thrombosis which gives rise to pulmonary embolism occurs either in the large systemic veins of the pelvis or of the lower extremities. Aschoff (26), on the basis of the gross characteristics of fatal pulmonary emboli, believed that most of them must have had their origin in a femoral vein. According to Homans (27), there is another site of thrombosis which may be a source of embolism, namely, the deep pelvic plexuses about the prostate and bladder in the male and the uterine veins and pampiniform plexus in the female. Rössle (40) and Neumann (41) have published the results of extensive series of pathologic-anatomic investigations in which they postulate a dominant role played by the plantar veins and the veins of the calf as the site of origin of thrombosis. In addition, Frykholm (29) has found that there are two more areas in which thrombosis tends to occur, namely, the veins of the adductor musculature of the thighs and the visceral pelvic veins. From these foci thromboses apparently follow the direction of the blood stream into the larger calibered veins. According to Homans, there are present between and beneath the great flat muscles of the calf and leg, plexuses of veins incompletely used except in times of great activity and capable of nourishing a rather extensive thrombosis without any apparent interference with the venous return of blood. Important evidence has been presented by Hunter, Sneed, Robertson and Snyder (42). These authors routinely removed and examined at autopsy the soleus and gastrocnemius muscles from a large number of adolescents and adults. In their series of 351 autopsies the incidence of thrombosis of the deep veins of the leg was 52.7 per cent. Thrombosis occurred especially among middle-aged and older persons confined to bed for varying periods of time. Fatal pulmonary embolism was responsible for 3.13 per cent of all deaths in their series; in 45.4 per cent of the cases of death from such embolism the most probable source was thrombosed leg veins. These workers believe that although fulminating emboli often spring from the femoral vessels, thrombosis here represents an extension from older clots in the legs and feet, and that lesser emboli migrate from the veins of the calf. Despite their small size, these emboli, by buckling and coiling, are capable of occluding even the major pulmonary arteries.

Based on venographic studies, which comprise a brilliant new chapter on the subject, Bauer (43) has also come to the conclusion that thrombo-embolic disease

almost invariably starts in the great deep veins of the lower leg. This development of the subject will be considered fully in a later section.

Ochsner (44) makes a distinction between "thrombophlebitis" with its clear-cut signs of inflammation, and "phlebothrombosis" in which clinical signs and symptoms are minimal or absent. However, Welch and Faxon (45) state that there are all gradations from purulent thrombophlebitis to pure thrombosis in which temperature, sedimentation rate and white count are normal, and while a few cases can be clearly defined as either phlebothrombosis or thrombophlebitis, the majority are equivocal. They emphasize that it is important to recognize, however, that the more closely the symptoms and signs approach those of true phlebothrombosis, the more dangerous is the situation as regards the release of the thrombus and hence the possibility of pulmonary embolism.

The literature places emphasis on the belief that pulmonary embolism occurs most often without clinical manifestations of a pre-existing venous thrombosis. According to Conner (49), the characteristic local signs of thrombophlebitis appear only after the occlusion of the vein has been complete and periphlebitic inflammation added. Often the first sign that a thrombosis is present is its migration (Patey (46)). The majority of Belt's (7, 24) cases of pulmonary embolism came to autopsy without recognition of the primary thrombosis during life. In a series of 897 cases of pulmonary embolism, Barker, et al. (47) found that in only 227 (25.3 per cent) was thrombophlebitis diagnosed clinically. There were 343 cases of *fatal* pulmonary embolism; in only 51 (14.9 per cent) did the antecedent thrombophlebitis present clinical manifestations. Four hundred and five (45.2 per cent) of all cases of embolism, and 135 (39.4 per cent) of fatal embolism showed neither clinical nor necropsy evidence of venous thrombosis respectively, and 265 (29.5 per cent) of all cases of embolism presented necropsy evidence but no clinical evidence of venous thrombosis. In McCartney's (8) experience, clinical evidence of thrombosis is not often observed in postoperative cases resulting in pulmonary embolism.

In Table 6 we have listed the possible foci of origin of the emboli in our series of fatal pulmonary embolism, based upon clinical manifestations and post-mortem findings. In only 13 of the 88 cases were there local clinical symptoms or signs which could be interpreted as indicating the presence of thrombosis or thrombophlebitis. These included unilateral edema of a lower extremity, pain, redness, tenderness or cord-like thickening in the legs, and thrombophlebitis at the site of cut-down intravenous infusions in the upper or lower extremities. The latter as the origin of fatal pulmonary embolism has also been reported by Strauss (48).

In two of our cases, the first and only clinical indication of the source of the embolus was pain in the calf of one leg just prior to the onset of the symptoms of the fatal embolism. The pain occurred 15 minutes before the fatal seizure in one case (Case 3), and 45 minutes in the other (Case 22). Presumably the pain was caused by the detachment of the embolus from the vein and the time interval represented the period of migration of the embolus from the leg to the pulmonary artery.

TABLE 6

Location of the Possible Origin of Pulmonary Emboli

CASE NO.	CLINICAL EVIDENCE	POST-MORTEM FINDINGS
1	Not available	Right common iliac vein (?)
2	" "	Right internal iliac vein
3	Pain in the right calf, 15 minutes prior to onset of the fatal pulmonary embolism	Free flow of blood from right femoral vein on pressure; no flow from the left
4	Not available	Not obtained
5	" "	Right spermatic vein; prostatic plexus
6	" "	Both renal veins; left ovarian vein
7	Right antecubital phlebitis and left lymphangitis at the ankle, both the sites of "cutdown" intravenous infusions	Right anterior cubital vein
8	Left saphenous phlebitis at the ankle, the site of "cutdown" intravenous infusion	Both common iliac veins; left internal iliac vein (?)
9	Not available	Right iliac vein
10	" "	Inferior vena cava at level of hepatic vein
11	" "	Not obtained
12	" "	Both external iliac veins (?)
13	" "	Not obtained
14	" "	Right renal vein (post-nephrectomy)
15	" "	Not obtained
16	Pain in left thigh, 36 days prior to the fatal pulmonary embolism	Right auricular appendage
17	Not available	Not obtained
18	" "	Stumps of uterine and ovarian vessels (post-hysterectomy)
19	" "	Not obtained
20	Edema of left leg, 2-3 weeks before death	Old aneurysm of cardiac apex with adherent thrombus
21	Not available	Left ovarian vein; right hypogastric vein (post-hysterectomy)
22	Pain in left calf, 45 minutes prior to fatal pulmonary embolism	Smaller branches of left femoral vein
23-24	Not available	Not obtained
25	" "	Small adherent thrombi in the right auricular appendage and wall of the right ventricle
26	Inflamed tender area on dorsum of left foot, diagnosed as phlebitis	Left saphenous vein
27-35	Not available	Not obtained
36	Left femoral phlebitis, 1½ years previously; right brachial phlebitis, 2 weeks ante-mortem; deep phlebitis of the right calf, one week ante-mortem	Left femoral vein; both common iliac veins
37-45	Not available	Not obtained
46	" "	Hepatic vein and adjacent inferior vena cava

TABLE 6—Concluded

SE O.	CLINICAL EVIDENCE	POST-MORTEM FINDINGS
7	Not available	Periprostatic venous plexus. Left femoral, external and left common iliac veins
18	Pain in the right leg with popliteal tenderness, 7 days ante-mortem; "drawing" sensation, 1 month previously	Periprostatic plexus; left femoral and external iliac veins
19	Not available	Both iliac veins
20-55	" "	Not obtained
56	" "	Junction of both iliac veins
57	" "	Right hypogastric vein at its junction with the external iliac
58-62	" "	Not obtained
63	Edema of the left leg	Left femoral and common iliac veins
64	Not available	Left femoral vein does not bleed on pressure
5-67	" "	Not obtained
68	" "	"The leg veins are distended and feel nodular." (No dissection, however).
69	" "	Not obtained
70	" "	Right renal vein, with extension into inferior vena cava (perinephric abscess).
71	Pain in feet and legs 10 days, antemortem; pain in left calf, next day, and edema of the legs on the following day	Right external jugular vein (?); right femoral vein
72	Thrombosis of the right internal saphenous vein in the thigh; tenderness in both calves; phlebitis in left calf (pain, tenderness, and swelling)	Left femoral vein
73	Not available	Not obtained
74	" "	Left femoral vein and all its branches
75	" "	Right common iliac vein
76	" "	Not obtained
77	" "	Edema of left leg
78	" "	" " " "
79-82	" "	Not obtained
83	Left internal saphenous vein cord-like and tender, 4 months prior to and on admission	" "
84-88	Not available	" "

Only 9 of the above 13 cases revealed a related thrombus or thrombophlebitic focus at autopsy. However, limited autopsy permission makes impossible any worth-while data. There were 20 cases in which thromboses were found at post-mortem examination which could possibly be considered the sites of origin of the pulmonary emboli but in which there were no clinical manifestations to indicate their presence during life. The important (predominant?) rôle of the

veins of the lower extremities can be seen from a study of the table (table In 45 cases there was neither clinical nor post-mortem evidence of the primary thrombosis. As indicated above, the lack of necropsy findings of the primary thrombosis in our series may be explained by the limited autopsy, dissection of the extremities not being possible in most instances.

It is generally held that the greater the local reaction accompanying a venous thrombosis, the less the likelihood of detachment of large emboli (Belt (7). If there is an inflammatory reaction of sufficient intensity in and around a vein to create local manifestations (thrombophlebitis), the thrombus probably is securely attached and only small portions are apt to be detached. Furthermore, a thrombus completely occluding a vessel would not tend to become detached as readily as a thrombus attached at a relatively small area (McCartney (8).

According to Bowen (50), the clinical phenomena of thrombophlebitis are referable to a clot which is not friable, and only small emboli will probably be thrown off. Thus, fatal embolism is rare but infarctions are common under such circumstances. In a group of 87 cases of postoperative phlebitis reviewed by Brown (51) fatal pulmonary embolism did not occur in a single instance whereas pulmonary infarction was recognized in 33 per cent.

Based on an exhaustive analysis of their large series of cases of postoperative venous thrombosis and embolism, Barker (47) and his co-workers suggest the following conception: "Postoperative venous thrombosis occurs in episodes and there may be only one episode. If this occurs in a small vein, part or all of the thrombus may detach soon after its formation to cause a small (non-fatal) embolus. If it is not detached or if only part of it is detached, the clinical signs and symptoms of thrombophlebitis develop in the involved vein. A second episode may occur in which the thrombosis propagates into a larger more proximal vein and this episode may be characterized by detachment (a larger or fatal embolus) by the development of thrombophlebitis in this vein, or by a small non-fatal embolus and thrombophlebitis. If the first episode of thrombosis occurs in a large vein as in the iliofemoral, the first and only signs of its occurrence may be sudden fatal embolism, iliofemoral thrombophlebitis may develop which can be recognized clinically, or a small fragment of the thrombus may be detached to form an embolus and iliofemoral thrombophlebitis may develop. Thrombosis may occur in both legs simultaneously or episodes may occur first in one leg and later in the other or in veins in other parts of the body. At the onset of any episode of thrombosis, embolism may occur. After thrombophlebitis has developed and existed for more than three or four days, the thrombus does not detach to form an embolus, but embolism may occur if a new thrombus forms in a proximal vein or in a vein elsewhere in the body."

Varicose veins, as a rule, are not regarded as an important etiologic factor in the production of the primary thrombosis from which pulmonary embolism is derived. As stated by Homans (27), thrombosis of varicose superficial veins tends to remain confined to the varicose veins and rarely progresses into the femoral vein or gives rise to embolism. Nevertheless, it cannot be denied that

perforated varicose veins may comprise the source of a primary thrombosis from which blood clot propagates into the deeper veins and breaks off to become an embolus. Thus, there are case reports in the literature of fatal pulmonary embolism following injections of sclerosing fluids into varicose veins (Dean and Dulin (52), McPheeters and Rice (53), Silverman (54), Kettel (55), Westerborn (56), Nunn and Harrison (57), Vaughn and Lees (58), and others).

To be continued

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LIFE'S LATER YEARS

STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[New York City]

PART 3*

THE ANCIENT HEBREWS

Give glory to thy father with thy whole heart; and forget not the pangs of thy mother. Remember that of them thou wast born; and what wilt thou recompense them for the things that they have done for thee?

Ecclesiasticus, Chap. VII.

A new translation of the Bible has been made available in recent years by James Moffatt (1) in an effort "to offer the unlearned a transcript of Biblical literature in the light thrown upon it by modern research. The Bible is not always what seems to those who read it in the great prose of the English version or, indeed, any of the conventional versions." The present writer has been attracted to the Moffatt translation by its clarification of hitherto obscure passages, such as Ecclesiastes XII: 1-8. All quotations are therefore from Moffatt's rendering, and bring not only new wording but often new meaning to the familiar verses.

In the enlightening introduction to his work, Moffatt speaks aptly of the "little library, which we call the Old Testament." As revelation and inspiration to untold millions, as ethical guide, as lawgiver, as history and literature, it has long lived up to its title as *The Book*. It has been studied by scholars for centuries for its contributions to the most varied fields of interest. There is a large body of literature devoted only to its medical aspects (2). For our present study the Bible has abundant meaning. In its pages we read descriptions of old age and learn the precepts laid down for the guidance of the Jews in their attitude to the old. The meaning of old age to the individual himself is discussed from many viewpoints.

Historically it must be emphasized that the books of the Old Testament are not older than the eighth century B.C., and some are as recent as the second century, B.C. The older ones are thought to represent the literary preservation of more ancient traditions. All show evidence of the fusion of parallel stories, of editorial changes and of elements taken over from other civilizations.

In Genesis (XLVII, 8-9) we find in the audience accorded by Pharaoh to Jacob as Joseph's father, a striking contact of the Egyptian and Hebrew viewpoints on longevity, and are able, as Miles (3) has pointed out, to read more significance in the brief lines than is at first apparent.

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Then Joseph brought his father Jacob in, and placed him before the Pharaoh. Jacob saluted the Pharaoh. The Pharaoh asked Jacob, "How many years have you lived?" Jacob answered, "For a hundred and thirty years I have had a wandering life of it; few and hard have been the years I have lived; fewer than the years my father lived and wandered." Then, saluting the Pharaoh, Jacob withdrew from his presence.

In view of the respect of every Egyptian for advanced age and his desire to attain the maximum of 110 years, Jacob must surely have impressed the Pharaoh. Certainly his humility of expression avoids the suspicion of boasting. Milne emphasizes that "both Jacob and the Pharaoh received renewed sense of the breadth and the continuity of life from the social experience," and that "in fact interracial friendship was here balancing itself on longevity as a pivot-point common interest."

From a medical viewpoint certain observations are essential. The knowledge of hygiene shown in the Bible is far ahead of that of medicine proper. The Mosaic Code, establishing a day of rest, regulating labor, promulgating the dietary laws, and attempting to prevent and treat pestilence and venereal diseases was a unique achievement in its own time, and stands on its merits even today. The cause of disease was sought in the anger of the Lord, and its cure to be found in sacrifice, repentance, fasting and prayer for Divine forgiveness. According to Neuburger, "the Old Testament, true to its strict monotheism, frowns on all belief in the demonic origin of disease, a belief universally prevalent among all people who attained to a certain cultural stage." By 22 B.C. the belief in God as the cause of disease and at the same time its healer had been reconciled with the actual practice of medicine, as we learn from the words of Ecclesiasticus (4) who point out in the greatest of all tributes to the physician, that there is place for medicine and prayer, since both have been created by the Lord.

In the early chapters of the Book of Genesis, the vital statistics, if taken literally, indicate an amazing length of life for Adam and his descendants. Noah is said to have died at the age of 950 years and the far-famed Methuselah prolonged his existence to 969 years. It is clear that the figures either imply the exaggeration often associated with mythical personages, or are based on some long forgotten calendar. When individuals of somewhat greater historical solidity appear, such as Abraham, Isaac and Jacob, the figures more nearly approach the plausible, being 175, 180 and 140 respectively, while Joseph lived to 110 years, Aaron to 123 and Moses to 120. The celebrated words of the Psalmist indicate a life span which approximates present-day experience.

Our life is seventy years at most, or eighty at best; a span of toil and trouble, soon over, and we flit away.

Psalm XC: 10.

The Book of Proverbs (16: 31) indicates the manner of attaining old age: "*Grey hairs are a crown of honour, gained by a good life.*"

In the Bible one finds objective reference to old age based usually on sound

observation. Commonly mentioned are weakness of vision, loss of sexual power and mental deterioration.

"Well," said the Eternal, "I will come back to you next Spring, when your wife Sarah shall have a son." Sarah was listening behind the door. She and Abraham were old, well on in years and the custom of women had ceased with Sarah. So Sarah laughed to herself, "Imagine marriage bliss for a worn old creature like me with an old husband."

Genesis 18: 20.

Now when Isaac was an old man, his eyes so dim that he could not see, he called his son Esau and said to him, "My son." Esau answered. "Here I am." He went on: "I am an old man now. I do not know how soon I may die."

Genesis 27: 1-3.

Moses was 120 year old when he died, but his eyes were undimmed and his vigor unabated.

Deuteronomy 34: 7.

Brim (2) in commenting on this passage points out that the Hebrew words *lo nuss lecho*, rendered as "his vigor unabated," means literally "his secretions did not escape"; and reminds us how very characteristic of old people are such weaknesses as lachrymation, salivation, rhinorrhea, urinary frequency and incontinence.

King David was an old man, well advanced in years, and although they covered him with bedclothes he could not keep himself warm. So his attendants said to the King, "Let some young girl be sought for my lord, the King, let her wait upon the King and take care of him: let her lie in your bosom, that my lord, the King may get warmth." All over Israel they sought for a beautiful maiden, and found Abisag of Shunem, whom they brought to the King; she was most beautiful, and she took care of the King and attended to him. But the King had no intercourse with her.

1 Kings: 1.

We are indebted to McKenzie (5), whose *History of Health*, 1758, is a valuable source book, for an interesting collection of commentaries on this famous passage. Referring to David and Abishag, McKenzie considers this method "a very proper means to warm and cherish him, and which when kept within the bounds of innocence and decency is justified by the opinions of Galen, Paul of Aegina, Francis Bacon, and Boerhave." "Nothing contributes so much to a good digestion as a sound healthy human body touching the stomach." (*Galen, Meth. med., lib. 7, cap. 7* and *De Simpl. med. facult. lib. 5, cap. 6.*) "It is very difficult to relieve a person who is cold and dry at the same time; and a plump healthy boy to lie in his bosom is one of the best remedies he can use." (*Paul of Aegina, Lib. 1, cap. 72.*) Lord Verulam recommends fomentations of living animals for the coldness of age (*Hist. vit. et mort. p. 300*). Boerhave frequently told his pupils

that an old German prince in a very infirm state of health, being advised to lie between two virtuous young women, grew so healthy and strong that his physicians found it necessary to remove his companions. In Hufeland's version (6) of the Boerhave story it was an old burgomaster of Amsterdam who enjoyed such a remarkable recovery as a result of this treatment. Cohansen (1749) in *Hermippus Redivivus or the Sage's Triumph over Old Age and the Grave, wherein a Method is laid down for prolonging the Life and Vigour of Man*, devotes a volume to the efficacy of the breath of young girls in furthering longevity.

Eli was ninety-eight years old, and his eyes were so dim that he could not see.
1 Samuel 4: 15

He is told of the disastrous outcome of the battle, the death of his two sons and the capture of the Ark of God by the Philistines.

When he mentioned the Ark of God, Eli fell back from his seat by the gate; his neck was broken, and he died—for he was old and heavy.
1 Samuel 4: 18

Barzillai the Gileadite ranks among the truly great old men of history because he wisely knew his own limitations, and declined King David's invitation to spend his remaining years in Jerusalem.

How many years have I to live, that I should go up with the King to Jerusalem? I am now eighty years old. Have I a taste for pleasure? Can your servant taste what he eats and drinks? Can I still hear the voice of singing men and women? Why, then, should your servant be a burden to my lord, the King? Pray let your servant return, that I may die in my own town, near the grave of my father and mother.

2 Samuel 19: 34-37.

We are also told of the last illness of Asa, Solomon's great-grandson, who long ruled wisely and devoutly as King of Judah:

In the thirty-ninth year of his reign Asa's feet became diseased; the disease was very painful, and Asa had recourse to his physicians, not to the Eternal. Asa slept with his fathers, dying in the forty-first year of his reign.
3 Chronicles 16: 12-13.

This illustrates the conflict between divine or priestly healing and the practical physician,—a conflict not settled until much later by Ecclesiasticus.

Two familiar tales from the Apocrypha must have brief mention here since they round out the picture of the character of old men, since one celebrates their perfidy and the other their nobility. The story of Susanna's false accusation by the lecherous elders and her acquittal by Daniel's intervention have inspired painters from Rembrandt van Rijn to Thomas Benton; and even today the narrative moves one to sympathy for the wronged woman and to disgust at the vile old men.

In contrast stands Eleazar the scribe (Maccabees, ii, chap. vi), who chose death

rather than renounce his religion by eating swine's flesh, even though his jailers out of pity, begged him only to go through the motions. "For it becometh not our years to dissemble," said he, "that through this many of the young should suppose that Eleazar, the man of fourscore years and ten, had gone over into an alien religion; and so they, by reason of my dissimulation, and for the sake of this brief and momentary life, should be led astray because of me, and thus I get to myself a pollution and stain of mine old age."

The attitude towards parents and older people in general is clearly set forth in the Old Testament. It is made part of man's duty to God and appropriate rewards are promised. The Fifth Commandment (Exodus 20: 12) states emphatically, "Honour your father and your mother that you may have a long life in the land which the Eternal, your God is giving you." On this sentence has depended for over 2,000 years our mores regarding the old. In Leviticus (20: 9) it is more drastically phrased, "For any one who curses his father or his mother, his blood be on his own head"; and again more softly, (19: 32), "You shall rise up before a man with white hair and honour the person of an old man."

A gentle plea is voiced by the Psalmist (70: 9-10), "Cast me not off in my old age, forsake me not when my powers fail." In Ecclesiasticus many admonitions are given relating to the duties of children to their parents, of which these are typical:

Dishonor not a man in his old age; for some of us are also waxing old.

Miss not the discourse of the aged; for they also learned of their fathers; because from them thou shalt learn understanding and to give answer in time of need.

In thy youth thou hast not gathered, and how couldest thou find in thine old age? How beautiful a thing is judgement for gray hairs, and for elders to know counsel? How beautiful is the wisdom of old men, and thought and counsel to men that are in honour! Much experience is the crown of old men; and their glorying is the fear of the Lord.

For the other side of the picture, youth resenting age, we turn to the Book of Job, where Elihu the son of Barakel the Buzite "blazed out in anger against Job for making himself to be better than God," but also against the three friends for compromising God by failing to refute Job.

*I am young and you are aged men;
So I held back; afraid to tell you my opinion.
I felt the word lay with a long life, and years
entitled men to instruct wisely,
Yet God inspires a man, 'tis the Almighty who
breathes knowledge into him;
It is not always seniors who are sage, or aged
men who understand.*

Job 32: 8-16

It is clear from the vehemence and stringency of the admonitions and the violence of the penalties, that there was an active tendency on the part of the young people in the opposite direction, and that the early Hebrews were not far removed from the days when the summary disposal of the old and weak was a necessary condition of existence. That this was particularly common among nomadic tribes has been emphasized by Sumner (6).

Among the many precepts laid down in the Mosaic Code, only one bears on the relation of age to working capacity. In Numbers 8: 24-30, we find that the Levites who enter upon their duties in the Tabernacle at the age of twenty-five, are relieved of active service after fifty. They may assist, but are not required to perform any duties.

The general attitude throughout the Bible toward old age is one of great pessimism; it is inevitable, it is distressing, and after life is done, there is nothing more.

*Poor man! his days are like grass,
He blooms like a flower in the meadow;
At the breath of a breeze it is gone,
And its place never sees it again.*

Psalms 103: 15-16.

*My days are few! let me alone awhile,
that I may have life bright with a brief smile,
Before I leave it to return no more.*

Job 10: 20.

The great poetry from the mouth of the unknown preacher of Ecclesiastes sums up the futility of life, and describes the infirmities of age in one of the most noted utterances of all time.

*But remember the Creator in the flower of your age,
ere evil days come on,
and years approach when you shall say,
"I have no joys in them;"
ere the sun grows dark,
and the light goes from moon and stars,
and the clouds gather after rain;
when the Guards tremble in the home of Life,
when its upholders bow,
when the maids that grind are few and frail,
and ladies at the lattice lose their lustre,
when the doors to the street are shut,
and the sound of the mill runs low,
when the twitter of birds is faint,
and dull the daughters of song,
when old age fears a height,
and even a walk has its terrors,*

*when his hair is almost white,
 and he drags his limbs along,
 as the spirit flags and fades.
 So man goes to his long, long home,
 and mourners pass along the street,
 on the day when the silver cord is snapped,
 and the golden lamp drops broken,
 when the pitcher breaks at the fountain,
 the wheel breaks at the cistern,
 when the dust returns to earth once more,
 and the spirit of God who gave it,
 Utterly vain—such is the speaker's verdict,
 everything is vain.*

Ecclesiastes XII: 1-8 (8).

These lines, so long considered as the epitome of pessimism, seem to have found an answer in the words of one who probably lived only some hundred years later than the Unknown Preacher. In the wisdom book called Ecclesiasticus, from which so many opinions about the old have been quoted, we read a courageous, robust admonition to all men, a message of understanding and compassion, founded in a truly religious spirit.

O death, how bitter is the remembrance of thee to a man that is at peace in his possessions, unto the man that hath nothing to distract him, and hath prosperity in all things, and that still hath strength to receive meat! O death, acceptable is thy sentence unto a man that is needy, and that faileth in strength, that is in extreme old age, and is distracted about all things, and is perverse, and hath lost patience! Fear not the sentence of death; remember them that have been before thee, and that come after; this is the sentence from the Lord over all flesh. And why dost thou refuse, when it is the good pleasure of the Most High? Whether it be ten, or a hundred, or a thousand years, there is no inquisition of life in the grave.

XLi: 24.

These quotations *in extenso* are revealing as an insight into a traditional attitude which reflects the spirit of the times, but they have a far greater significance in that, with the rise and spread of Christianity, they became the foundation for all priestly and lay thinking for nearly twenty centuries, and today constitute a vital part of our intellectual heritage. The contribution of the Old Testament writers to our present historical narrative has therefore less strictly medical significance, and more of a religious, ethical and philosophical bearing. As a matter of fact, the emphasis of the Old Testament on the frailty of the human body and the futility of life acted during the Middle Ages to impede and hinder medical progress. Taken in the broader aspects, however, this review refreshes our memory of the wisdom of our forebears and strengthens our feeling of kinship and continuity with men whose essential problems and conflicts differed but little from our own.

The writer is indebted to his life-long friend and teacher, Rabbi Nathan Krass, for helpful advice and encouragement in the preparation of this chapter.

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INTRACRANIAL MENINGIOMAS¹

AVRAAM T. KAZAN, M.D.²

and

DANIEL WELLER, M.D.³

[*New York*],

JORGE GOMEZ JARAMILLO, M.D.⁴

[*Medellin, Colombia, S. A.*]

Tumors derived from the meningeal coverings of the brain are among the more common types of brain tumor. Moreover, they are among the intracranial neoplasms which lend themselves to successful surgical removal. A knowledge of their pathologic and clinical behavior is essential if an early diagnosis, a prerequisite of satisfactory surgery, is to be made. It is advisable therefore to utilize all available data—gross anatomical, histological, and clinical—for a better understanding of the behavior of such tumors. A review of the current workable concepts relative to the above features serves as the main theme of this paper. It is accompanied by a presentation of illustrative cases observed on the neurological and neurosurgical services and studied in the neuropathology laboratory of The Mount Sinai Hospital in New York.

Until recently there was great diversity of opinion as to the origin and classification of meningiomas. The greater number of observations were of a descriptive character and resulted in the many different names which were applied by different investigators to tumors of similar structure. This led to the accumulation of unreliable morphologic data and the classification of meningiomas was in a chaotic state. In the past twenty-five years increased and more precise information became available on the origin and histologic variability of these neoplasms, and in 1935 Globus (1) presented his theory as to the formation of meningiomas and offered his histologic classification. This theory, we believe, made possible a clearer insight into the true nature of this type of tumor and the varying pattern often assumed by it.

Using an approach based on the phylogenetic and ontogenetic processes underlying the development of the meninges, Globus points out that meningiomas arise from the meningeal primordium—the skeleto-neural intertissue—which incorporates not only the forerunners of the several layers of the mature meninges but also the cranial endosteum. Therefore, these tumors may acquire the histologic features of any one of the meningeal layers and may even include bone traceable to the endosteal primordium. The skeleto-neural intertissue is represented early in the development of the embryo by a layer of undifferentiated

¹ From the Neuropathology Laboratory, The Neurological and Neurosurgical Services of The Mount Sinai Hospital, New York.

² Former Resident in Neurology, The Mount Sinai Hospital, New York, now Lt. A. T. Kazan, MC, A.U.S.

³ Voluntary Assistant in Neuropathology, Mount Sinai Hospital, New York.

⁴ Fellow, Dazian Foundation for Medical Research.

mesenchyme which completely envelops the medullary tube and lies between it and the ectoderm. During subsequent stages in the developmental process a further differentiation of this mesenchyme takes place so that there is distinguishable an inner zone of condensation, the endomeninx, closely adherent to the nervous tissue; and an outer layer, the ectomeninx which lies subjacent to the newly-forming skeletal tissue. As growth proceeds the endomeninx splits incompletely to become the vascular pia and the epithelial-like arachnoid. On the other hand, the ectomeninx or the outer layer divides into the endosteum and the dura (fig. 1). Although many of these developmental stages are recognizable in the cyclostomes, fishes, amphibians, reptiles, birds and mammals, as we ascend the phylogenetic scale the division into layers becomes more complete. In the amphibians and reptiles the ectomeninx splits into an endosteum and dura, while

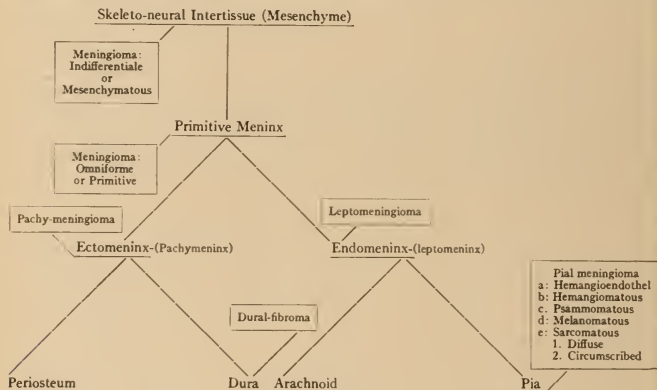


FIG. 1. Classification of meningiomas (from Globus: "The Meningiomas")

the endomeninx remains a single layer. In birds and mammals, on the other hand, the endosteum and dura undergo an early refusion to form a secondary dura and the endomeninx splits into pia and arachnoid.

It is evident, then, that since all meningeal elements (i.e., endosteum, collagen fibres of the dura, arachnoid epithelium, and vascular pia) can spring from a common source, many histologically different neoplastic patterns may be derived from the same source. Actually one type of tissue usually dominates the histologic picture. It is characteristic of the meningiomas that their histologic classification is determined by the predominance of derivatives of one or another primitive meningeal layer. Accordingly, meningeal tumors are termed "leptomeningiomas" if their histologic picture is dominated by leptomeningeal derivatives; on the other hand, the preponderance of the vascular pia in certain instances establishes the lesion as a "hemangioma". Despite the apparent

occurrence of outspoken types of meningiomas, many vague transition patterns exist so that no sharp demarcation can be made between the simple and more complicated forms.

HISTOLOGIC CLASSIFICATION

Basing his work on the above presented facts, Globus (1) suggested the following scheme for the histologic classification of the meningiomas.

TYPE I—*Mesenchymatous meningioma*. This tumor duplicates the structure of the primitive mesenchymal tissue; the cells are irregular in shape; their nuclei are well stained. They show no definite arrangement. The blood vessels resemble the channels found in the pia of the embryo. Areas of liquefaction with pseudo "foam-cell" formation may be detected. The tumor appears to be encapsulated by the leptomeninges which, at some points, send prolongations into the interior of the growth (figs. 2 and 3).

TYPE II—*Meningioma omneforme*. In this tumor all of the elements of the primordium may be present in greater or lesser degree. Areas of bone formation are mingled with zones of a mesenchymatous pattern, and accumulations of arachnoidal rests and collagenous fibres similar to those seen in the normal dura are common. The arachnoidal cells may be seen in whorl formation or arranged in sheets. Foam-cells, psammoma bodies and pigment carrying cells are not infrequently found. The vessels are represented by well developed capillaries reminiscent of the young structures of the pia. Bone may often be found irregularly distributed throughout the tumor (figs. 4 and 5).

TYPE III—*Pachymeningioma*. Bundles of collagenous fibres which predominate throughout the tissue characterize these tumors. They are also called "fibroblastic meningiomas" or "dural fibroblastomas". Occasionally, among the collagen bundles, will be found areas of bone formation as well as many degenerating capillaries and psammoma bodies. Sarcomatous degeneration may take place, in which case mitotic figures and even giant cells are noted (fig. 6).

TYPE IV—*Leptomeningioma* (arachnoid meningioma). Usually the arachnoid "epithelium" plays the most important role in the structure of these tumors. The cells are spindle-like, round or oval in shape and are clustered in whorls forming alveolar groups separated by blood channels. This mixture of primitive arachnoidal cells and remnants of pial vessels led Globus to emphasize the term "leptomeningioma" rather than "arachnoid meningioma"; the latter would tend to exclude the important part of the pia in the formation of the tumor. Occasionally there occurs a definite orientation towards the vascular form with small cysts and islands of mononuclear or multinuclear giant cells. The tumor then becomes a transitional form of leptomeningioma (fig. 7).

TYPE V—*Meningioma piale* (vascular meningioma). This type of tumor is made up almost exclusively of pial components: capillaries, foam cells, and sinusoids. There are several subtypes:

1. *Hemangioendotheliomatous*: This tumor resembles hemangioendotheliomas found in other parts of the body. It is not encapsulated. The primitive vascular endothelium seems to form the gradual transition between the tumor and the

brain tissue. In some parts are seen areas of cells rich in chromatin. The capillaries are abundant and the walls of the blood vessels may be either thick or thin (fig. 8).

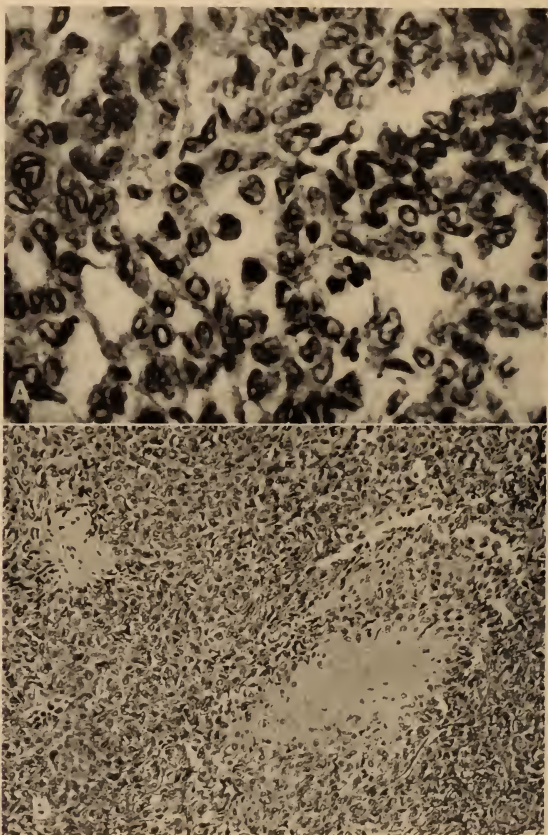


FIG. 2. Mesenchymatous meningioma. A. Appearance of primitive polymorphous and hyperchromatic cells ($\times 420$). B. Areas of liquefaction ($\times 340$).

2. *Hemangiomatous*: The vessels are more mature and some of them present a high degree of degeneration. They may be of small caliber or, on the contrary, like dilated channels assuming the character of cavernomas (fig. 9).

3. *Psammomatous*: Psammoma bodies are the dominant histologic feature. These bodies are found in the normal meninges and, although they have been looked upon as vascular buds, they probably represent blood vessels with degeneration and calcification of their walls. They give the appearance of small horls disseminated through the microscopic field (fig. 10). This variety is usually benign. According to the records of The Mount Sinai Hospital most of these tumors originate from the meninges of the spinal cord.

4. *Melanomatous*: This is a rare subtype of meningioma with melanin-bearing cells the characteristic feature. They are found mixed with other cellular elements of dural or leptomeningeal derivation (fig. 11).

TYPE VI—*Sarcomatous meningioma*: This is a transitional form of meningioma ending towards a more malignant type. Yet all the types previously described

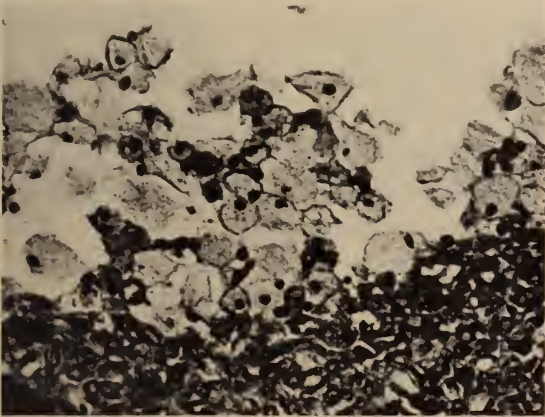


FIG. 3. Mesenchymatous meningioma. Characteristic "foam cells" ($\times 420$)

may, at times, acquire a malignant orientation. This is especially true of tumors of pial derivation. Sarcomatous meningiomas appear to be predominantly vascular in their structure, with wide channels surrounded by endothelial cells of anaplastic appearance. Mitotic figures and giant cells are prominent (fig. 12).

TOPOGRAPHIC AND GROSS ANATOMIC FEATURES

The gross anatomic features of meningiomas are in some ways just as important as the histologic patterns adopted by them. In studying the various shapes assumed by these tumors one is impressed by the influence of the bony architecture of the skull upon them. Insofar as meningiomas may arise from any point of the dura or leptomeninges, they will manifest variations in size and shape peculiar to the given site of origin and to the restrictions that the region places upon the growth of the neoplasm. Accordingly, olfactory groove tumors are

usually flat as a result of being compressed between the floor of the anterior fossa and the frontal lobes, while sphenoidal or petrous ridge tumors may straddle

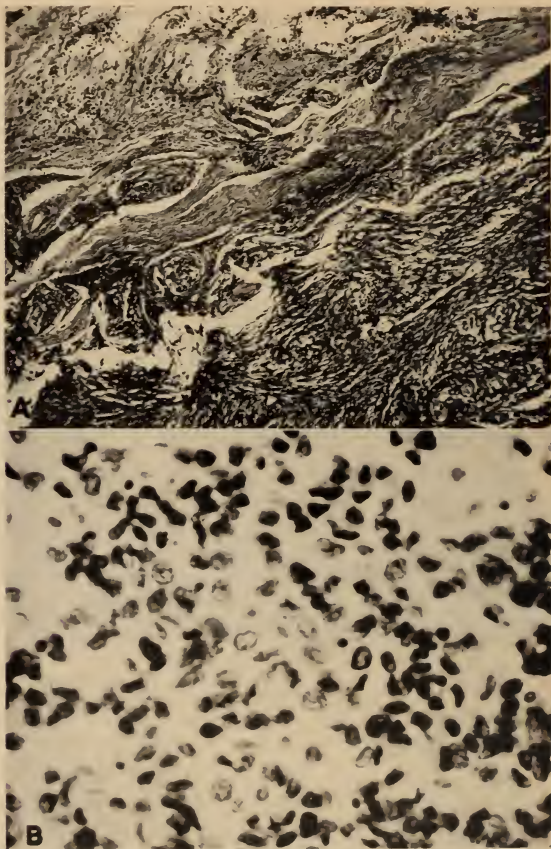


FIG. 4. Meningioma omneforme. A. Collagenous fibrous tissue ($\times 150$). B. Area of mesenchymatous tissue ($\times 420$).

these bony prominences. On the other hand, meningiomas arising from the deeper extensions of the pia within the cerebrum do not suffer such great restric-

ons to their expansion and therefore tend to be spherical or ovoid in shape.
In addition to the types mentioned above, there is the meningioma "*en plaque*",

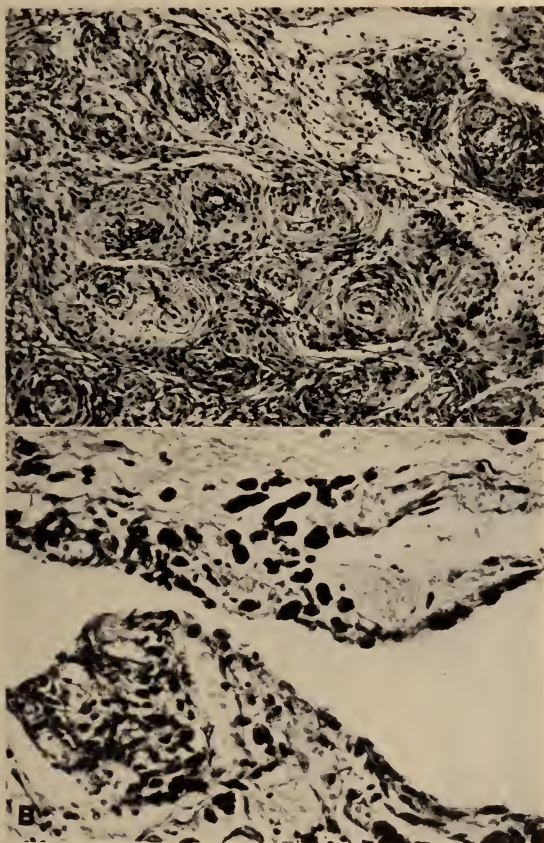


FIG. 5. Meningioma omneforme. A. Whorls enclosing small vessels ($\times 170$). B. Area of melanoblastic tissue ($\times 400$).

a disc-like form assumed by certain slow-growing neoplasms found chiefly in the pterional region.

Meningiomas may be pedunculated, sessile, smooth-surfaced or nodular. The variation in size attained is realized on comparing the small pea-sized suprasellar

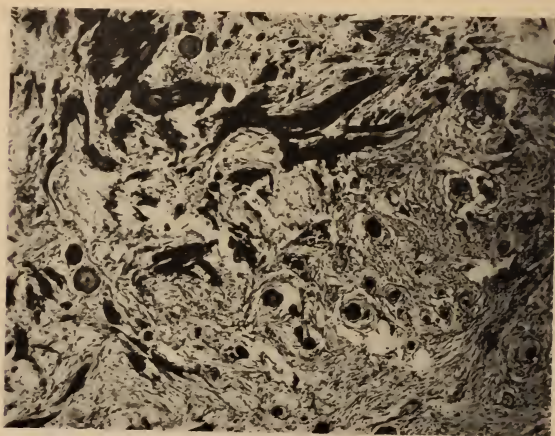


FIG. 6. Pachymeningioma containing psammoma bodies ($\times 120$)

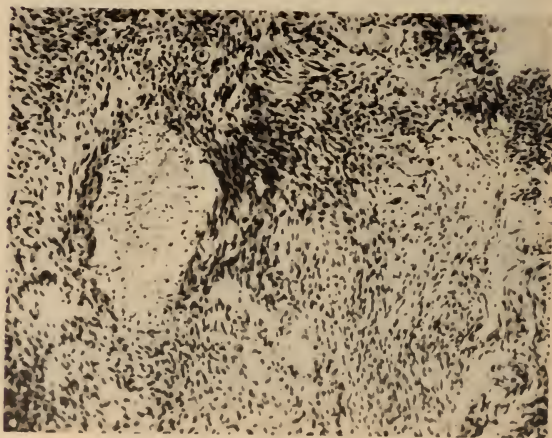


FIG. 7. Leptomeningioma containing islands of "foam cells" ($\times 160$)

tumors with the huge ones often found in the frontal or other regions. As to their consistency, these tumors may be firm or soft, the former type more often

being found in the basilar regions. At times they may undergo cystic degeneration. Not infrequently they cause edema of the surrounding tissues, giving rise

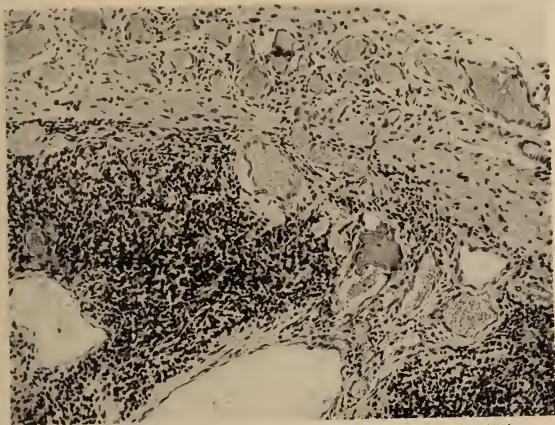


FIG. 8. Meningioma (pial) hemangioendotheliomatous ($\times 150$)

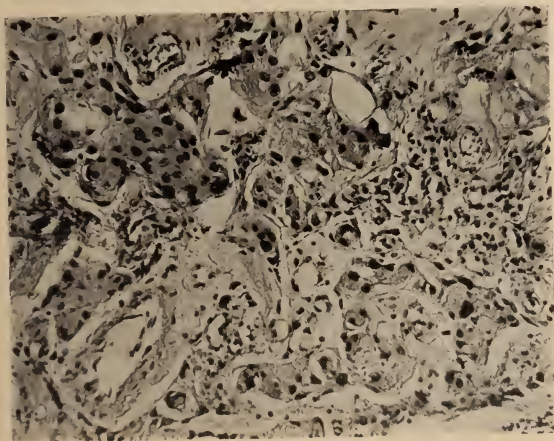


FIG. 9. Meningioma (pial) hemangiomatous ($\times 200$)

to symptoms out of proportion to and far more extensive than those one would expect from their actual size. Frequently meningiomas are associated with great enlargement of cerebral, meningeal and even scalp blood vessels.

Of clinical importance is the effect of the tumors on adjacent bone: they are capable of causing erosion, absorption, hyperostosis or eburnation of bone either

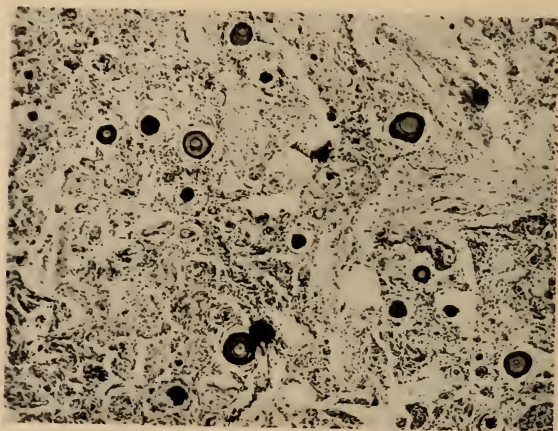


FIG. 10. Meningioma (pial) psammomatous ($\times 100$)

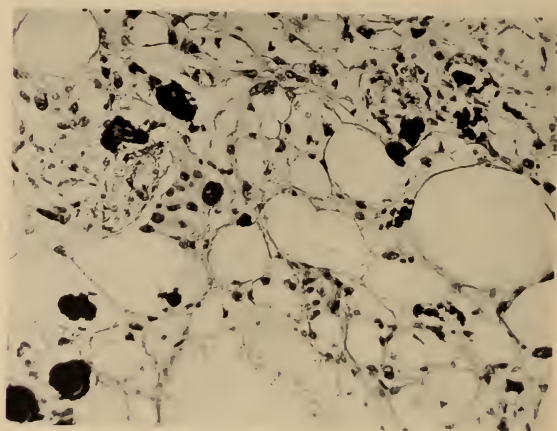


FIG. 11. Meningioma (pial) melanomatous ($\times 200$)

through actual infiltration of the Haversian canals or by the reactive hyperemia they provoke. These local alterations in bone density are detectable by palpa-

on or by roentgenologic examination and often help in the diagnosis and localization of the lesion. Attention has already been called to the phylogenetic and togenetic hypothesis of Globus explaining the formation of bone within the

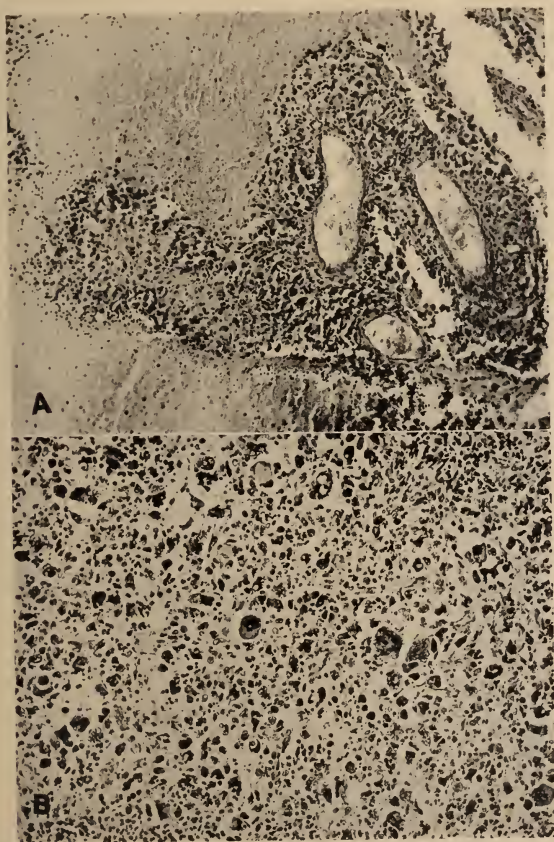


FIG. 12. Sarcomatous meningioma. A. Perivascular cell arrangement ($\times 205$). B. Giant cells ($\times 105$).

actual substance of these tumors; this phenomenon witnesses the origin of the meninges and endosteum from a common anlage. The so-called dural tumors situated over the convexities were formerly regarded as respecting the integrity

of the brain, but Globus (1) has shown that they may pass through the pia way of the blood vessels and infiltrate the underlying brain. There is no record of their having penetrated the galea aponeurotica in the opposite direction involve the scalp.

Distant metastases from meningiomas are extremely rare. In all of Cushing's experience (2) he noted only one such case. This patient had undergone seventeen operations for the removal of the primary growth and its various recurrences; she finally died thirteen years after the original craniotomy. At necropsy several small nodules histologically similar to the primary focus in the brain were found in the lungs of the patient. Another instance has been described (3) in which metastases to bones, lungs and adrenals occurred from a sarcoma of the meninges. In the latter type of tumor, however, the more common mode of dissemination is by seeding. Frequently there is gravitation of malignant cells down into the spinal canal where large secondary deposits may be set up.

CLINICAL CLASSIFICATION AND ILLUSTRATIVE CASES

A clinical classification of intracranial meningiomas was first proposed by Cushing (4) in 1922 and put into its definitive form by him in 1938 (2). It is by far the best available classification. His cases fell into three large (regional) and one small (miscellaneous) groups as outlined below. Since only the large groups of tumors give rise to recognizable clinical syndromes, they alone will be considered here.

- | | |
|--|---|
| <p>A. Convexity meningiomas</p> <p>I. Lateral⁵</p> <p>a. Precoronal</p> <p>b. Coronal</p> <p>c. Postcoronal</p> <p>d. Pararolandic</p> <p>e. Parietal</p> <p>f. Temporal</p> <p>g. Occipital</p> <p>II. Parasagittal</p> <p>a. Hyperostosing (flat)</p> <p>b. Non-hyperostosing (global)</p> <p>III. Falcial</p> <p>C. Posterior fossa meningiomas</p> <p>I. Basilar groove</p> <p>II. Cerebellar³</p> <p>III. Cerebello-pontile angle</p> | <p>B. Meningiomas of the base</p> <p>I. Olfactory groove</p> <p>II. Suprasellar</p> <p>III. Sphenoidal ridge</p> <p>a. Inner third</p> <p>b. Middle third</p> <p>c. Outer third</p> <p>1. Global</p> <p>2. "En plaque"</p> <p>IV. Infratemporal</p> <p>V. Cavum Meckelii</p> <p>VI. Peritorcular</p> <p>VII. Cranial nerves</p> <p>D. Miscellaneous</p> <p>I. Without dural attachment</p> <p>II. Multiple meningiomas</p> <p>III. Diffuse (e.g., sarcomatosis)³</p> |
|--|---|

CONVEXITY MENINGIOMAS

Meningiomas of the convexities have traditionally been divided into four groups corresponding to the four major lobes of the brain: frontal, parietal, temporal and occipital. No matter what the precise site of their origin, however, the tumors often give rise to signs and symptoms referable to more than one of

⁵ In these headings, the above system differs slightly from that of Cushing.

regions named. The reasons for this are obvious: meningiomas often attain very large size, overlapping several lobes; and even small tumors may be surrounded by wide areas of edema and brain destruction which interfere with the physiologic function of the parts involved just as effectively as a tumor might. While clinically the above classification may be satisfactory, from the viewpoint of preoperative localization it is inadequate. For example, 70 per cent of convexity meningiomas arise anterior to the Rolandic fissure, yet this whole area could ordinarily be designated simply as "frontal". To remedy this, Cushing¹) advocated dividing the frontal lobe at its mid-point, at a line corresponding to the projection on the brain of the coronal suture. This system uses a constant fixed landmark, an advantage which is not present when the gyri of the frontal lobe are used as orienting points.

Employing, then, both cranial and cerebral landmarks, Cushing catalogued convexity meningiomas into precoronal, coronal, postcoronal, pararolandic, parietal, temporal and occipital groups. Lesions in each of these areas are characterized by signs and symptoms which they provoke through causing alterations of the physiology peculiar to the region involved. Therefore, the presence of Jacksonian seizures, pyramidal tract signs, astereognosis, visual field defects, aphasia and personality changes each and all give clues to the probable site of the tumor.

Precoronal tumors are few in number, representing only about 10 per cent of convexity meningiomas. They originate in that half of the frontal lobe lying between the frontal pole and the projection on the brain of the coronal suture. Because they originate in a "silent area", they have no clear-cut symptomatology and are characteristically innocuous until they produce general symptoms due to their great bulk. Marked mental changes appear only when the tumor has invaded a large part of one frontal lobe and has begun to distort the other. "Witzelsucht", euphoria with a tendency toward punning, is quite characteristic. Choked disc with optic atrophy, contralateral weakness, Jacksonian seizures, hemiparesis with hypotonicity, grasp reflex, and anosmia are among the manifestations of the tumor which ultimately present themselves.

Case 1. Precoronal meningioma.

History (Adm. 217015; P.M. 3903). A man, aged 42 years, was admitted to The Mount Sinai Hospital on March 2, 1922. Beginning one year before admission, he noticed a progressive tremor of his left hand. Three months later he began to have headaches and vomited occasionally. At the same time, he became aware of a slow-growing lump situated in the right frontal area. One week before admission he developed incontinence of urine and noted a tendency to stumble.

Examination. There was a soft, tender, pulsating egg-shaped mass over the right frontal region. The patient was markedly euphoric. Speech faculties were intact. Sense of smell, unfortunately, was not described. Eye examination disclosed bilateral exophthalmos; there was a high degree of myopia bilaterally but the fundi were normal. The pupils were irregular, reacted well to light. Weakness of both external rectus muscles was noted. Left central facial weakness was present. The patient was left handed. The grip of the right hand was weaker than that of the left and there was clumsiness in the execution of fine movements of the right hand. Deep reflexes were active and equal; abdominal reflexes

were absent. There was a positive Hoffmann sign on the right but there was no Babinski sign. Sensory examination was normal.

Course. It was thought that the patient was suffering from a primary bone tumor involving the underlying cerebral hemisphere. A lumbar puncture revealed normal cerebrospinal fluid. Roentgenologic examination of the skull revealed a definite round defect in the right frontal bone. An exploratory operation was performed and disclosed an inoperable tumor. The patient died on the day following operation.

*Necropsy findings.*⁶ *Brain. Gross:* The brain was edematous throughout. A tumor measuring 4 cm. in diameter and involving the right superior, middle and inferior frontal gyri was found (fig. 13). It was firm in consistence, irregular, somewhat nodular and had few large blood vessels on its surface. The shelling out of the neoplasm left behind only thin layer of white matter between the cavity and the ventricle.

Microscopic: Sections of the tumor⁷ revealed large fields of undifferentiated cells scattered without orderly pattern; these cells were closely packed, elongated and contained large round or oval nuclei. A few mitotic figures were found. There were many thin walled, blood-filled vascular channels throughout the tumor. Groups of foam-cells were found, usually located near the periphery of areas of disintegration (figs. 2 and 3).

Diagnosis. Mescenchymatous meningioma.

Comment. This case is included to bring out the variety and confusing nature of signs and symptoms accompanying meningiomas of the precoronal region. Disturbances in urinary function are not uncommon in frontal neoplasms. The exact mechanism of production is not known, but since they are usually seen in patients with personality changes such as euphoria or mental deterioration they may be due to these psychic changes. On the other hand, some authorities ascribe them to involvement of as yet undetermined bladder reflex arcs. In this series of tumors, erosion of the calvarium by meningiomas is rare and indicates a relatively malignant tumor type.

Coronal tumors arise from the meninges subjacent to the coronal suture between the bregma and the pterion. It is noteworthy that when they are grouped with the parasagittal, bregmatic and pterional tumors underlying other parts of this same suture they represent approximately one-third of all convexity meningiomas. Localizing signs, which are usually absent until late in the course of the tumor's growth, include contralateral progressive palsy of the arm and face with the leg remaining uninvolved. This rather important diagnostic point was noted in 11 of Cushing's 17 cases (2). Jacksonian seizures beginning in the face also occur. By the time the diagnosis is made, serious impairment of vision has often taken place; the prolonged elevation of intracranial pressure causes choked disc and secondary optic atrophy. The same mechanism may give rise to pseudo-localizing symptoms such as a secondary pituitary syndrome and more or less complete anosmia. Even signs of cerebellar ataxia result from involvement of the fronto-ponto-cerebellar pathways. Tumors on the left side produce psychic disturbances more often than those on the right. Subjective symptoms include headaches, blurring of vision, drowsiness, emotional instability, memory loss, and occasionally paraphasia. X-ray examinations at times reveal a definite

⁶ All post-mortem examinations except that of Case 6 consisted in examination of the head only.

⁷ Microscopic sections all stained with hematoxylin and eosin.

dostosis, but an area of increased vascularity along the coronal suture may be the only localizing sign.

Post-coronal tumors are few in number and overlie the posterior half of the frontal lobe between the coronal suture and the motor area. Among the multiplicity of signs and symptoms produced, those which will help to make the differential diagnosis are disturbances of conjugate gaze, contralateral vasomotor



FIG. 13. Precoronal meningioma—mesenchymatous (see Figs. 2 and 3)

disturbances, and Jacksonian fits of a motor type involving primarily the upper extremity. Roentgenologic evidences as described above may be found.

Pararolandic tumors lie along the Rolandic fissure in direct relationship to the primary motor and sensory projection centers. They are quite numerous and their position affords easy accessibility for surgical removal. They vary in size, but in contradistinction to precoronal tumors, most of them are detected and

removed while still small. This is because of the symptom-producing area in which they originate. Jacksonian fits are, of course, frequent and when the tumor lies in the dominant hemisphere they are often associated with speech defects. Convulsions may start in any part of the body and then spread in a characteristic pattern or "march" to adjacent areas. A sensori-motor aura, such as a painful contraction of the foot—or a sensory aura, such as the tingling of the arm, commonly inaugurates the convulsive episodes. Pararolandic tumors are not so prone to cause spasticity of the paretic limbs as are those more rostrally situated. Their tendency to recur, and their relative benignity are indicated by the 42 operations which had to be performed on eight patients treated for this condition in Cushing's series.

Parietal tumors lie between the post central gyrus and the posterior boundary of the parietal bone. They usually cause sensory Jacksonian seizures restricted to the face and arms; the foot, because of its representation on the mesial aspect of the hemisphere, is rarely primarily involved. Sensory changes are generally confined to subjective numbness and paresthesias associated with astereognosis and diminution of two-point and position perception in the limb in question (so-called "cortical discriminative" impairment). Low-lying tumors may involve the upper fibers of Meyer's loop, in which case a lower quadrantic field defect is noted. Lesions in the dominant hemisphere may cause a complete ("global") aphasia or give rise to subtotal manifestations such as anomia, alexia, finger agnosia, etc.

Temporal and temporo-sylvian tumors give rise to few symptoms unless they lie on the dominant side. Under these circumstances, about half of the cases will present some aphasic signs. On the other hand a quadrantic field defect—in this case characteristically in the *upper* visual field—may be the only evidence of abnormality; this is found in some 40 per cent of temporal lobe tumors. Occasionally the patients experience bizarre highly organized visual hallucinations, e.g., they may see "little brown men standing in the doorway". Of lesser diagnostic significance is the tendency of these tumors to provoke generalized or focal seizures, weakness and even paralysis of contralateral limbs.

Occipital lobe meningiomas are very rare. This is partly because they arise in the smallest of the cerebral subdivisions. They cause signs of increased pressure: papilledema, headache, vomiting and generalized convulsions at an early stage. More focalizing signs are: unformed visual hallucinations (flashes of colored lights) frequently appearing in homonymous fields, cerebellar signs (from pressure on subtentorial structures), and various degrees of blindness with hemianopic field defect.

PARASAGITTAL MENINGIOMAS

Parasagittal meningiomas are remarkable for the frequency with which they occur. They constitute a large number of convexity meningiomas (about 35 per cent). Like pterional tumors (q.v.), these may induce a hyperostosing reaction of the overlying skull, and so have been classified into flat hyperostosing and global non-hyperostosing types. Only the latter will be considered here, because

primarily manifests itself through its effect on the brain. The former type gives rise to huge bony deformity of the skull, but usually causes only minor central nervous system signs and symptoms.

Global non-hyperostosing meningiomas are found arising from any point along the longitudinal sinus from the crista galli to the torcula Herophylli. They are commonly found to be intimately adherent to the dura and may extend down along the falx. Those originating from the anterior two-thirds have a somewhat better prognosis than the ones from the occipital third, because should either minor or surgical intervention cause obstruction of the longitudinal sinus, less circulatory damage ensues in the case of anteriorly-placed tumors. Meningiomas of the middle or paracentral area are detectable at an early stage because of the characteristic seizures they provoke. These convulsions are Jacksonian, usually begin in the foot or toe and "march" cephalad. Pyramidal tract signs in the legs and urinary incontinence or retention are late evidences of paracentral bulge pressure. On the other hand, diminished position sense and disturbances of spatial orientation in the leg are common and fairly early manifestations of cortical involvement. Anterior third tumors are characterized by headache, choked disc, secondary optic atrophy, personality changes, impaired memory and euphoria. Convulsions are far less frequent in this group, appearing in only about one-third of cases. Tumors of the occipital third may give advanced choking of the disc and homonymous field changes. Premonitory symptoms of headache, nausea and vomiting usually precede the visual field defects.

Case 2. Parasagittal meningioma.

History (Adm. 351104; P.M. 8778). M. C., a woman, aged 52 years, entered The Mount Sinai Hospital on April 18, 1933 with an eight month history of personality changes consisting of self-neglect and euphoria. During that period she developed a voracious appetite and gained 50 pounds in weight. She also complained of intermittent severe right fronto-occipital headaches not associated with nausea or vomiting. Four months before admission vertigo appeared, her gait became unsteady and she noted a tendency to fall toward the right. For about a month before admission there was weakness of the right side of the body, dragging of the right side of the face and dragging of the right foot.

Examination. The patient was very obese. The skull was tender to percussion over both frontal areas. Mentally she was obtunded but euphoric; insight was very poor. Her gait was spastic and she tended to drag her right foot. Bilateral papilledema was present. Deep reflexes were hyperactive throughout; abdominal reflexes were diminished on the left and there was a questionable Babinski sign on that side.

Course. Lumbar puncture was not done because of evidence of increased intracranial tension. On roentgenologic examination of the skull marked absorption of the posterior clinoids was noted. Ventriculography disclosed displacement of the ventricular system to the left with deformity on the right lateral ventricle. On the basis of these films a diagnosis of right frontal lobe neoplasm was made. Total protein of the cerebrospinal fluid obtained from the left lateral ventricle during this procedure was 17 mg. per cent. At operation a tumor mass the size of a plum was removed from the medial aspect of the right frontal lobe. The patient's postoperative course was not unusual, but on the tenth postoperative day she developed a bronchopneumonia and the following day she expired.

Necropsy findings. *Brain.* *Gross:* The brain was edematous. A large excavation was found in the medial surface of the right frontal lobe; this measured about 4 cm. in diameter and was filled with blood clot. On sectioning the brain a large tumor mass was found buried

in the substance of the right hemisphere (fig. 14). It extended from a point about 2 cm back of the frontal pole as far posteriorly as a point on the level of the foramen of Monro. The tumor was granular in appearance, well demarcated from the surrounding brain tissue. It appeared to be encapsulated on its free surface and was attached to the falx. At its periphery it was highly vascular.

Microscopic: A section revealed loosely arranged whorls of cells containing elongated and flattened nuclei with cytoplasm drawn out into strands. Among these cells there were numerous oval cells with eccentric nuclei and foamy granular cytoplasm. In one-half of

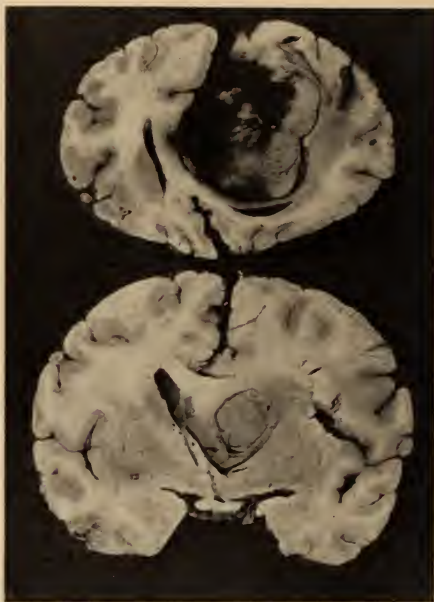


FIG. 14. Parasagittal meningioma—pilo hemangioendotheliomatous

the section there were numerous areas of necrosis and hemorrhage. Numerous small vascular channels were present throughout the section.

Diagnosis. Meningioma piale, hemangioendotheliomatous.

Comment. There are several points of interest here. The paradoxical gain in weight so often found in frontal lobe neoplasms is noted; whether this is due to personality changes with physical lethargy, to bulimia, or to secondary hypothalamic changes it is hard to say. It is well known that cerebellar signs occur in 25-50 per cent of frontal lobe tumors, presumably from involvement of the cortico-cerebellar tracts. Before the introduction of encephalography, this not

frequently led to diagnostic errors. Finally, the marked right-sided pyramidal tract signs and left Babinski sign in a right cerebral neoplasm might be confusing. Recalling that they are due to the pressure of the left-sided neoplasm on the contralateral leg area, they are not difficult to understand.

MENINGIOMAS OF THE FALX CEREBRI

These tumors are not common. Though they always originate in the midline, they may expand predominantly toward one side or become bilaterally symmetrical. Like parasagittal growths, they have been grouped into anterior, middle and posterior third tumors; those of the sub-bregmatic areas occur most frequently. They show considerable variation in size and may weigh as much as 300 Gm. Many are concealed, necessitating a transcortical approach after their depth and position have been ascertained by exploratory punctures.

Their symptomatology differs little from that of parasagittal tumors. Those originating in the middle third of the falx have a tendency to cause Jacksonian attacks involving the legs; as the tumors increase in size they initiate signs of pyramidal tract involvement. It is not unusual to find paraparesis simulating cord neoplasm in large centrally placed tumors. Lesions of the anterior third, again, may cause choking of the discs and secondary optic atrophy associated with personality changes. Those of the occipital third produce complete homonymous hemianopsia and often advanced papilledema. Headache, vomiting are common to all. Other diagnostic aids are the downward and backward displacement of the pineal body and the distortion of the ventricles as detected by x-ray and aerographic studies.

Case 3. Meningioma of the falx cerebri.

History (Adm. 348715; P.M. 8677). C. S., a man, aged 44 years, entered The Mount Sinai Hospital in March 1933 with a history of periodic frontal headaches for 4 years, and periodic convulsive seizures involving the whole right side for about $1\frac{1}{2}$ years. In the year before admission his vision began to fail, his speech became slow and halting, and he had difficulty finding the right words. Ten months later the patient's right arm and leg became weak and he noted a tremor of the right arm. This persisted until admission.

Examination. The patient was dull and emotionally unstable. There was bilateral papilledema, the left pupil was larger than the right and both were sluggish in their reaction to light. Visual fields were normal. A right central facial paresis was found. There was weakness and hyperreflexia on the right side.

Course. Lumbar puncture on admission yielded cerebrospinal fluid under an initial pressure of 200 mm. of water; total protein was 108 mg. per cent. X-ray examination of the skull showed an enlarged sella with thinned out posterior clinoid processes; vessel markings of the calvaria were exaggerated. The frontal bones were thickened and there was calcification of the falx. The patient was observed in several Jacksonian attacks on the ward, but no characteristic "march" of convulsive movements was noted. Operation for an interfrontal tumor, predominantly on the left side was performed; the procedure was not completed, however, because of the drop in the patient's blood pressure. As the patient did not emerge from the stupor after operation, a secondary exploratory operation was performed but the tumor was not located. The patient expired the following day.

Necropsy findings. *Brain.* *Gross:* A firm spherical mass about 6 cm. in diameter was found in the dorsal part of the left fronto-parietal area (fig. 15). The tumor was adherent throughout its length to the homolateral surface of the falx cerebri in proximity with the

superior sagittal sinus. It was well demarcated from the adjacent brain tissue but was surrounded by an area of edematous tissue.

Microscopic: The section revealed cells of varying size with round vesicular nuclei they were arranged in circles, clumps or whorls. Numerous polygonal spaces containing a thin homogenous material were present. There were many irregular vascular channels and strands of fibrous tissue scattered throughout the section (fig. 9).

Diagnosis. Meningioma piale, hemangiomatous.

Comment. The clinical course is typical of most tumors involving the rostral end of the motor area. The greatly enlarged sella is a not uncommon finding in cases of chronic increased intracranial pressure. It has no focalizing significance. An important finding was the calcification in the tumor as revealed by x-ray.

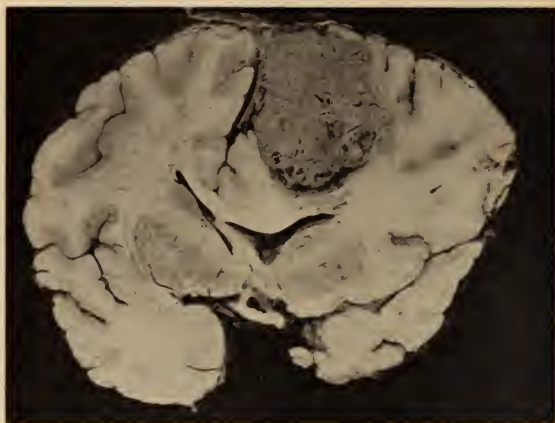


FIG. 15. Facial (cerebral) meningioma—pial hemangiomatous (see Fig. 9)

examination; calcification is a fairly common finding in the normal falx, but in this instance it had a specific pathologic significance.

MENINGIOMAS OF THE OLFACTORY GROOVE

These tumors arise from the basilar meninges at the junction of the cribriform plate and the planum sphenoidale (fig. 16-1). They are very vascular and often attain great size. They frequently affect the olfactory nerves, optic chiasm, frontal lobes and anterior cerebral arteries and thus may cause anosmia, visual defects, nerve-head changes, alterations in personality, memory impairment, and pyramidal tract signs on the contralateral side, most marked in the leg. Unilateral anosmia and blurred vision accompanied by a corresponding pallor of the nerve head should suggest the possibility of this lesion. The Foster Kennedy syndrome of retrobulbar neuritis and primary optic atrophy on the side of the lesion, with papilledema on the contralateral side has been described as occurring

th tumors found in this region. Roentgenologically, calcification of the tumor and depression of the sphenoidal bone or the mesial floor of the anterior fossa may be detected. The vascularity of this neoplasm and the frequent involvement of the anterior cerebral artery make surgical removal hazardous.

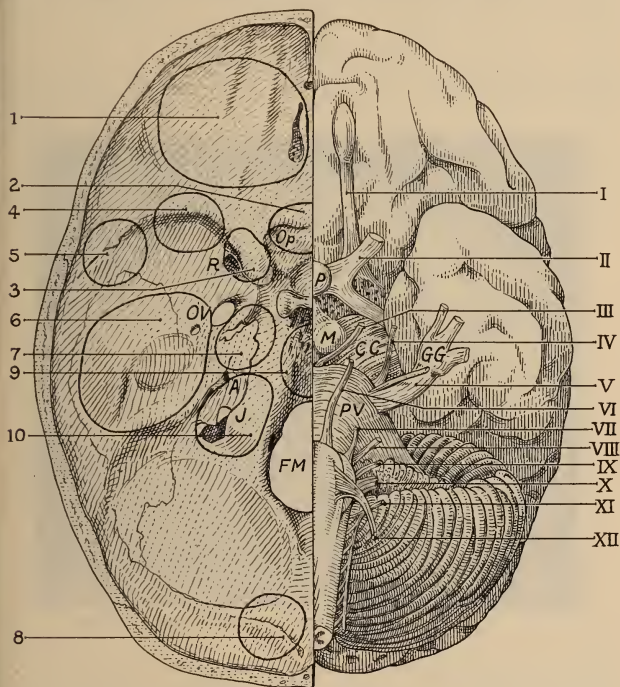


FIG. 16. Schematic figure designed to show relationship of meningeomas of base of skull to structures of base of brain. Cranial nerves (I-XII) enumerated on right, sites of common basal meningeomas (1-10) on left. Foramina: OP, optic; R, rotundum; OV, ovale; A, internal auditory; J, jugular; FM, foramen magnum. Structures of base: P, pituitary; M, mammillary body; CC, crus cerebri; GG, Gasserian ganglion; PV, pons Varolii.

Case 4. Olfactory groove meningeoma.

History (Adm. 218792; P.M. 3973). L. S., a man, aged 46 years, entered The Mount Sinai Hospital on May 27, 1922. Three years prior to admission he began to have dizzy spells which were sudden in onset and rapidly proceeded to loss of consciousness. On several occasions the patient remained conscious but felt the left side of his body "becoming stiff." These attacks occurred one to three times a week. Additional symptoms were

occasional headaches, diplopia, gradual deterioration of personality and progressive impairment of memory.

Examination. The patient showed marked emotional instability. Sense of smell was diminished bilaterally. There was papilledema and early optic atrophy of both discs, more advanced on the right. The pupils reacted sluggishly to light but well in accommodation. Slight facial weakness was present on the left. The left knee and ankle jerks were more active than those on the right; the left abdominal reflexes were sluggish. A positive Babinski sign was found on the left.

Course. A diagnosis of right frontal lobe neoplasm was made. Lumbar puncture disclosed clear cerebrospinal fluid under slightly increased pressure; no cells were present. Although a ventriculography was tried, it could not be completed because the patient developed dyspnea and faint convulsive movements of the right arm. A right frontal

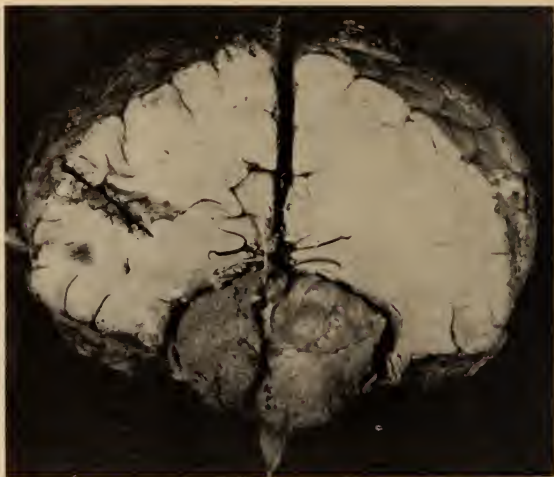


FIG. 17. Subfrontal meningioma—leptomeningioma

craniotomy was performed but owing to the precarious condition of the patient no extensive procedure could be followed and the tumor was not disclosed. During the operation the patient went into shock; he expired the following day.

Necropsy findings. Brain. Gross: On exploring the undersurface of the frontal lobes a tumor was found. It was roughly circular in shape and measured about 2 inches in diameter. Ventrally it involved both olfactory tracts, while dorsally it displaced upward and laterally the inferior surface of each adjacent frontal lobe (fig. 17). It was soft, reddish, could be readily separated from the left frontal lobe. Portions of the right frontal lobe, cribriform plate and orbital plate appeared to be invaded by the growth.

Microscopic: Sections of the tumor showed many closely packed elliptical cells with elongated nuclei. Whorls were numerous and often showed central necrosis. There was a moderate amount of connective tissue between the cell groups.

Diagnosis. Leptomeningioma.

Comment. The very fact that syncopal attacks and focal convulsions occurred for three years suggests the presence of a meningioma. By the time the patient presented himself for treatment, the diagnosis was obvious. The hyposmia, optic nerve changes, and left pyramidal tract signs indicated a right frontal lobe lesion. The advanced personality changes, however, reflected frontal involvement.

SUPRASELLAR MENINGIOMAS

These are firm global tumors that arise from the tuberculum sellae or the sulcus chiasmaticus (fig. 16-2). They may vary in type from a small innocuous asymptomatic nodule to a large pernicious mass which distorts adjacent structures. Until the neoplasm reaches about 1 cm. in size, the results following surgical removal are usually good; however, this is not so in those cases where marked compression of the chiasm has taken place. The so-called "chiasmal syndrome" consists of primary optic atrophy with bitemporal field defects in the presence



FIG. 18. Suprasellar meningioma—pial psammomatous (see Fig. 10). Tumor arising from posterior wall of sella.

of a normal sella turcica in adults. This picture has been considered pathognomonic of suprasellar meningiomas, but all too frequently the clinical status is indefinite. The optic nerves seldom show positive atrophy, and the field defects may not be unequivocally bitemporal. Evidences of hypothalamic involvement such as polyuria and polydipsia, obesity, and menstrual changes occasionally inaugurate the picture. In some cases the tuberculum sellae and the anterior clinoids may be eroded. Globus (5) feels that the difficulty in the early and accurate diagnosis of these tumors lies in the fact that there is an abrupt transition from the asymptomatic stage to the one giving rise to widespread symptoms.

Case 5. Suprasellar meningioma.

History (Adm. 403808; P.M. 10272). A woman, aged 32 years, entered The Mount Sinai Hospital in March 1937 complaining of amenorrhea for 2½ years and failing vision for one year. During the four months before entry, she had hot flushes several times a day followed by episodes of vomiting. She had also noted protrusion of the left eye-ball.

Examination. The left eye was more prominent than the right and the extraocular movements on the left were limited. Corrected visual acuity was 10/200 on the left and

20/30 on the right. By confrontation there was a temporal hemianopsia on the left. The fundi showed marked myopia associated with secondary degenerative retinal change. There was no definite optic atrophy. The right knee jerk was more active than the left. The abdominal reflexes were absent. There were no pathologic reflexes.

Course. The laboratory studies were of particular importance. Lumbar puncture was omitted advisedly. Basal metabolic rate was minus 17 per cent. Janney test was normal (glucose-tolerance test). Charting of the visual fields disclosed a loss of vision in the temporal half of the left visual field with a beginning quadrantic defect in the superior nasal field on the same side. A second charting six weeks later showed in addition a large central scotoma in the right visual field. X-ray examination of the skull revealed no changes in the sella. An encephalogram revealed incomplete filling but no displacement of the lateral ventricles. The cisterna chiasmatica was also incompletely filled. A left transfrontal craniotomy was performed after six weeks in the hospital. A large tumor was exposed on the floor of the anterior fossa in the region of the sella. The tumor could not be completely removed, for it extended around the free margin of the wing of the sphenoid to disappear within the sella. The patient expired the day following the operation.

Necropsy findings. Brain. Gross: On lifting the frontal lobes, a neoplastic growth was found protruding upward from the sella (fig. 18). It measured about one inch in diameter and distorted the course of the optic nerves, but was not adherent to them. The right nerve was laterally displaced, while the left climbed over the surface of the tumor. When the main body of the tumor was removed, a small mass of tissue was seen to be protruding through the diaphragma sellae. It appeared to arise from the dural covering of the posterior wall of the sella. The sella itself was of normal size, but the posterior wall was thickened and the lateral walls were eroded. The pituitary body was compressed to 3×1.5 mm. and pushed deeply in toward one side of the sella. Another mass of tumor tissue was found in the area occupied by the left cavernous sinus; this measured 2.5×1 cm. It surrounded the nerves and blood vessels in this region and was in connection with the mass of tissue in the sella turcica through the eroded left lateral wall.

Microscopic: The tumor showed an abundant, somewhat vascular stroma permeating areas of very cellular tissue. Many psammoma bodies were present (fig. 10). The cells were oval, arranged in islands and showed a tendency to form whorls. The small vessels of the growth contained much calcium deposition in their walls. A section of the pituitary body revealed the tumor cells to be infiltrating it from one side; there was no capsule between the new-growth and the glandular tissue. Islands of arachnoid cells were found in the pars anterior of the gland.

Diagnosis. Meningioma piale, psammomatous.

Comment. The presence of visual symptoms in conjunction with endocrine disturbances and general symptoms of intracranial tumor suggests pituitary neoplasm. The origin of the growth apparently from the dura within the sella explains the early onset of amenorrhea. It is interesting to note that in spite of the site of origin of the tumor, and in spite of the extent of its suprasellar portion, the x-ray of the skull revealed no increase in the size of the sella. The involvement by the growth of the left cavernous sinus and associated nerves may explain the proptosis and the impairment of the extra-ocular movements on the left.

To be continued

Morris Manges

May 10, 1865-January 26, 1944

It was in the early eighties, while I had charge of a surgical clinic in the dispensary, now the Out-patient department of The Mount Sinai Hospital, when the day I needed counsel in one of my cases and sent one of my assistants to the department of internal medicine for aid. The response was made by Morris Manges who was in charge of the clinic that afternoon.

It was our first meeting and I was immensely attracted by his friendly smile and his obvious interest in the medical aspect of my problem. It seemed as if I must have known him for years; outside of our common professional occupation our tastes were similar. In but a few minutes of contact we found that our recreations of the summer vacation, the woods and streams were identical.

He became a frequent guest and a delightful companion in my Adirondack camp on beautiful Blue Mountain Lake where we fished for trout in the neighboring streams and explored the fragrant pine and balsam forests.

On attaining his degree in medicine from Columbia he spent two industrious years of study in Berlin and Vienna, returning for an internship in Charity Hospital. In 1892 he was appointed Visiting Physician to The Mt. Sinai Hospital. He was consultant until his death.

Dr. Manges seldom displayed the evidence of honors he had won in his academic and professional schools; I never saw him wear the Phi Beta Kappa key of the College of the City of New York which was his on graduation.

He was a facile writer and among his papers may be mentioned his edition of Ewald's work on Diseases of the Stomach, which he translated.

His practice rapidly grew and patients came from many parts of the United States, many of them to ask his opinion on health resorts in Europe. Because of his sympathetic manner and his diagnostic skill he soon became a prominent consultant.

Manges was an excellent teacher of clinical medicine and in this capacity was a valued professor in the New York Polyclinic and Medical School as well as in New York University and Bellevue Medical college.

Soon after The Mount Sinai Hospital was dedicated in its new Fifth Avenue home, an evening was set aside for a meeting to consider future development of the institution. The gathering was called by the president, Isaac Wallach, and he trustees, who invited the professional board and a number of distinguished guests from New York and other cities, to discuss and make suggestions. Only a few months ago, Dr. Manges called upon me and we recalled with interest that evening's program. He was then writing an article on Isaac Wallach for the Mt. Sinai Journal which appeared in the Anniversary number dedicated to Dr. Alfred Meyer (Jan.-Feb. 1944). We recalled that Isaac Wallach opened the program with a little lecture on the importance to the public of charitable



Morris Langer

ganizations and stressed the great value that scholastic education in our profession must have in the study of medicine and the healing of the sick.

At that time our hospital had no connection with any university or medical school and Wallach's speech made a profound impression on his hearers among whom there were several men from outside of New York; one of these was Sir William Osler of the Johns Hopkins University Medical school, a renowned professor, later of Oxford University. He made a strong plea for the type of education which our president had emphasized.

Among the avocational interests of Dr. Manges was his appreciation and study of art. He was a member of the American Physicians' Art Association and he exhibited some of his own work, in water colors at the exhibitions of that body. He gave most of his attention to painting out-door subjects. Perhaps his favorite pastime following his retirement was visiting the museums and the displays of art dealers. Less than a day before his sudden death he had spent hours at the Metropolitan Museum of Art, appraising one of the new exhibitions. The walls of his home were decorated with fine engravings and etchings while Japanese pictures, prints and drawings, were admirably displayed.

His library included many volumes illustrating an intimate knowledge of books by no means all medical and there were bound volumes of society reports of which he was a member, for example, the Archaeological.

Medals of bronze, principally French, were collected and he presented some of these to the writer.

His most important single donation he made to the Academy of Medicine. It was the first specimen in America of radium for therapeutic use which he imported from the Curie laboratory. A full account of this is in the Bulletin of the Academy of Medicine, November, 1930, by Archibald Malloch our valued and discerning librarian.

In his room in the Academy he showed me a little wooden box within which was another metal-lined paste-board container. After removing the lead covering from this second box it was opened and there, within, was still another receptacle of metal, about the size and shape of a cigaret. An opening in the end of the cigaret-shaped metal case was plugged by a blunt needle-like piece and an inscribed bit of paper indicated the weight of the precious element as .25 mg. No radium could be seen but Dr. Malloch said he had taken the container to Dr. Failla a physicist in the basement of the Memorial Hospital where there was a device for measuring radiation. To the joy of Dr. Malloch the indicating needle of the apparatus which by the way, had been invented by Dr. Failla, at once jumped to 4.25 so the radium must have been present and not lost as might have been suspected.

A portrait in oil of Dr. Manges is to be hung in one of the meeting halls of the Academy and it has been suggested that a plate be attached to the frame giving the facts about this valuable specimen, for the information of those who might see the portrait.

I hope that this little outline of my friend's biography may serve to bring some of his scientific, artistic and cordial attributes to the mind of the reader.

HOWARD LILIENTHAL, M.D.

Bernard Sachs

January 2, 1858—February 8, 1944

We come here, all of us, with love and reverence to take leave and bid God speed to a dear friend.

You have known him, so I can add little to what you know. You have been familiar, for perhaps scores of years, with his erect sturdy form, with his quick step, instinct with drive and purpose.

His light shone before men, and always to lead them and make easier the footsteps; and it shone the world over, wherever doctors met and talked together.

He radiated an old Roman Virtus;—as I once said, one could not stand with him for ten minutes in shelter from a shower and not perceive in him an uncompromising honesty and a forceful goodness.

His rare hesitations in speech or action came only from his fear that he might wound in inadvertence. A gentleman is said to be one who never hurts anyone unintentionally, and Barney Sachs could and did fight doughtily for his idea of the right against wrong-thinking and wrong-doing, but never, in most of a lifetime did I know of his being careless to a friend or colleague,—indeed often he suffered some foolish ones overlong.

His friends knew his wisdom and his honour; many bequeathed to him burden and great charges to be furthered when they themselves had left the scene of their endeavours,—and we know the scruple and keen effort he used to make the aims of those good friends live on among men.

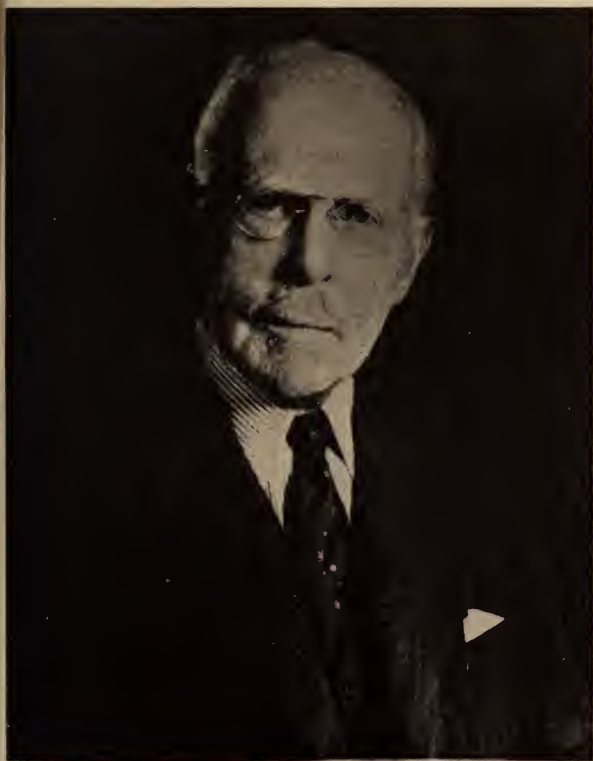
No honour was missing: to that within himself were added all those that could be given to one of our Profession; he was twice President of the American Neurological Association, President of the Academy of Medicine, and as President of the International Neurological Congress, he made American Medicine refulgent in Europe. To all these, and to duties to his City, and to his pursuit of literature he brought distinction of conduct and of word: but also, to each task he brought an immense energy which sprang, I know, from a great and unfailing love for his fellow man,—a love which, with his skill, cured and assuaged the sick, and comforted the afflicted. His last strength and affection were freely spent to aid the scholars who fled to the light of America out of Hitler's night.

He loved, he toiled, he served, he *led*,

"Nothing is here for tears, nothing to wail
or knock the breast; no weakness, no contempt,
Dispraise or blame; nothing but well and fair,
And what may quiet us in a death so noble."

FOSTER KENNEDY¹

¹ Eulogy delivered at the funeral services of Dr. B. Sachs, February 9, 1944.



Bernard Sachs

BERNARD SACHS

CURRICULUM VITAE²

The following record of the important events in the life of Dr. Bernard Sachs met with the approval of Dr. Foster Kennedy, who said, "I could not imagine a better account of his life than the Curriculum Vitae in the Anniversary Volume."

However, such an account cannot indicate that in spite of the increasing physical infirmities of old age, the intellect of this great man remained till the very end keen, active and receptive.

Sachs was thus fully aware and deeply appreciative of the well deserved honors that were bestowed upon him and, above all, of the added happiness brought to him during the last few years of an abundant life.—Ed.

Born, Baltimore, Md.	January 2, 18
Graduated from the Sach's Collegiate School.	18
Graduated from Harvard College, receiving A.B. degree with honors in natural history	18
Studied medicine in Strassburg and Berlin, receiving M.D. degree.	18
Worked as postgraduate student with Meynert at Vienna, with Hughlings Jackson at London and with Charcot at Paris.	1882-18
Instructor, New York Polyclinic Hospital.	18
Member of the American Neurological Association.	18
Neurologist, Montefiore Hospital.	18
Professor, New York Polyclinic Hospital.	18
Consulting Neurologist, The Mount Sinai Hospital.	18
President of the American Neurological Association.	18
President, New York Neurological Society.	18
Honorary Member Moscow Neurological Society.	18
Alienist and Neurologist to Bellevue Hospital.	18
Chief, Neurological Service, The Mount Sinai Hospital.	19
President, New York Neurological Society (second time).	19
Consulting Neurologist, The Mount Sinai Hospital.	19
President, First International Neurological Congress, Berne.	19
President of American Neurological Association (second time).	19
Professor, Clinical Neurology, College of Physicians & Surgeons, Columbia University	19
President, New York Academy of Medicine.	1933-19
Director, Division of Child Neurology, Neurological Institute.	19
Corresponding Member, Royal Society of Medicine, London.	19
Director, Child Neurology Research (Friedsam Foundation).	19
Senior-Consultant, Division of Neuropsychiatry, Montefiore Hospital.	19
Received special Anniversary Volume of the Journal of The Mount Sinai Hospital as a token of esteem from his colleagues, associates, pupils and admirers.	19
Memberships:	
American Medical Association	
American Neurological Association	
American Psychiatric Society	
American Association for Research in Nervous and Mental Disease	
Association of American Physicians	
New York Neurological Society	
New York Society of Clinical Psychiatry	
Fellow of New York Academy of Medicine	
Paris Neurological Society	
Moscow Neurological Society	
Royal Society of Medicine (section of Neurology), London	
Charaka Club	
Lotos Club, etc.	

² An extensive list of Dr. Sachs' publications and other contributions to the science and progress of medicine may be found in the Anniversary Volume (J. Mt. Sinai Hosp., Vol. 9 No. 4, 1942).

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Root Amputation Prior to Pulp Canal Filling. D. M. KOLLEN AND M. SCHWARTZ. J. Am. Dent. A. 29: 2178, December 1942.

This technique is described of treating anterior teeth with large periapical involvement, especially useful in army and defense dentistry, where neither prolonged drainage through pulp canal nor restorations are practical.

The method has been successfully employed since 1936 by the authors, and in carefully selected cases in anterior teeth, no failures have been noted as yet.

Briefly, it involves 1) the establishing of proper access to the pulp canal; 2) under local anesthesia, lifting the mucosa and exposing and removing buccal alveolar plate at the site of the apex of the root and, 3) removing the infected apex and curetting the periapical area; then enlarging, irrigating, drying and filling the canal, in one operative session.

Root amputations are usually removed after four or five days and normal alveolar regeneration has been demonstrated in our periodic roentgenographic follow-up.

Gastric Drip Therapy for Peptic Ulcer—A Summary of Ten Years' Experience. A. WINKELSTEIN, A. CORNELL AND F. HOLLANDER. J. A. M. A. 120: 743, November 1942.

Methods which are most effective in the neutralization of the free acidity throughout the hours of the day are most likely to be successful in the medical therapy of peptic ulcer. Since all previous methods of controlling the interdigestive secretion were found to be inefficient, particularly throughout the longest interdigestive period, viz., the night, the drip method of therapy was devised. The authors' studies have shown that both milk—sodium bicarbonate and alumina gel preparations are effective in raising the gastric pH from the average from 1.5 to 4.0. Since free acid does not exist above a pH of 3.5 and since 99 per cent of peptic activity is eliminated at a pH of 4.0. The digestive action of hydrochloric acid-pepsin mixture is practically eliminated, particularly during the night when other forms of medication are usually discontinued. A description of the drip apparatus and the technique of administration are given in detail. Therapeutic observations made since 1932 with a report of typical cases are included. These demonstrated that intragastric drip therapy is rational, practical, and that it produces prompt and more persistent results than other forms of therapy. Finally, the method gives the patient a means of self therapy at home for long periods during the night without interfering with his daily work.

Histochemical Demonstration of Amine Oxidase in the Kidney. K. A. OSTER AND N. C. SCHLOSSMANN. J. Cell. & Compt. Physiol. 20: 373, December 1942.

The conversion of cyclic amino acids to pressor amines by decarboxylase and the oxidative deamination of the amines to aldehydes by amine oxidase is of importance in the mechanism of experimental hypertension. Both enzymes hitherto manometrically demonstrated in minced kidney tissue only, may be localized histochemically in tissue sections. Para-hydroxy-phenylacetaldehyde the product of the oxidative deamination of tyramine by amine oxidase, gives rise to a blue stain with the aldehyde reagent of Schiff and Feulgen, chromatin sulfurous acid. The demonstration of this aldehydic product of enzymatic activity requires that all naturally occurring "plasmal" aldehyde in the sections be combined with sulfite and thus rendered FSA-negative. In sections of guinea pig kidney so treated, tyrosine oxidase activity appears to be localized in the distal convoluted tubules. When tyrosine is substituted for tyramine, the site of the aldehyde formation remains the same, indicating the presence of decarboxylase together with amine oxidase.

This technique confirms the absence of amine oxidase from rat kidney in concordance with results obtained with minced tissue. The significance of localization of these enzymes to a specific site in the nephron is discussed.

Influence of a Polished Rice Diet Upon Spontaneous Mammary Cancers in Mice Treated with Yeast Extract. R. LEWISOHN, C. LEUCHTENBERGER, R. LEUCHTENBERGER, D. LASKER AND Z. DISCHE. *Cancer Research*, 2: 818, December 1942.

In previous papers by the same authors the effect of intravenous injections of yeast extract on spontaneous cancer in mice has been reported. Complete disappearance of tumors following treatment was observed in 30 per cent of the animals. The authors have now combined intravenous injections of yeast extract with a diet of polished rice supplemented with carrot.

Before treatment was started a biopsy was performed on every animal, in order to insure an accurate diagnosis of malignancy. The changes which took place in the tumors following this combined treatment were entirely different from those observed when yeast extract alone was used. The tumors changed into a necrotic, often cheesy mass. A second biopsy specimen, taken about two weeks after the treatment was started, allowed a microscopic study of these changes. While the polished rice-yeast extract treatment is effective it provided an active yeast extract is used, inactive extracts fail to give results even with a polished rice diet. Control animals fed on polished rice and carrots, but without injection of yeast extract, did not show any complete regression. The average time required for complete disappearance of a tumor was reduced from 47 days (when yeast alone was used) to 20 days (when the combined treatment was employed). Among 25 carcinomas in Rottam mice treated with yeast and polished rice, 17 showed complete regression. In a set of 9 RIII mice complete regression was effected in 4 animals.

Sarcoid of the Face (Besnier-Boeck (Schaumann) Disease): Report of a Case. J. SCHROEDER. *J. Am. Dent. A.*, 29: 2208, December 1942.

A case report is given of a white woman, aged 48 years, who presented a firm irregular non-tender mass within the substance of the right cheek of four weeks duration. Biopsy of mass was reported as tuberculosis of cheek. The Ziehl-Neelsen test was negative, and complete medical work-up for tuberculosis was also negative. Under arsenical treatment the mass receded. Seven months previously the patient had a small mass in the right parotid region suggestive of a mixed tumor. Lipiodol study was made. Biopsy of this mass was reported as tuberculosis of the preauricular lymph node. Surgical intervention was advised but the patient refused treatment. The mass disappeared spontaneously. Because of the history and the absence of a positive diagnosis of tuberculosis the case presented as one of sarcoid of face.

An Eye for A Tooth. H. A. GOLDBERG. *New York J. Dent.* 12: 278, 1942.

A thorough knowledge of the dental-medical history is of utmost importance in determining what part infected teeth may play in relationship to systemic disease. The teeth and gums may harbor infection but may not be the direct cause of a systemic disturbance. The dental roentgenograms may or may not suggest infection. Nevertheless, these teeth must be looked upon as a possible focus of infection. It often requires exceptional diagnostic ability to prove that dental infection is the primary factor in systemic disease.

Teeth harboring infection should not be permitted to remain in the mouth. If this infection cannot be eradicated by treatment, these teeth should be extracted, as we never know when this latent infection may flare up, metastasize, and involve any tissue in the body.

The Steroids. H. SOBOTKA AND E. BLOCH. *Ann. Rev. Biochem.* 12: 45, 1943.

The present review deals primarily with the biochemistry of the oldest members of the steroids, namely, the bile acids and the sterols, and also with chemical reactions leading from these compounds of which there is an abundant supply, to substances of pharmaceutical significance, especially the sex hormones and cortical hormones, which are less accessible in nature.

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Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of the Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore 2, Maryland, or 1 East 100th Street, New York City.



SOME RECENT ADVANCES IN BACTERIOLOGY AND VIRUS RESEARCH WITH SPECIAL REFERENCE TO ELECTRON MICROSCOPY¹

GREGORY SHWARTZMAN, M.D.

INTRODUCTION

The vast progress recently achieved in bacteriology and virus research makes necessary to limit the scope of the presentation to some well-defined topics. The following subjects which may be of special interest to the clinician and the clinical bacteriologist will be taken up to-night:

An attempt will be made to define the viruses and survey some of the recent investigations.

Our understanding of viruses may be aided by the recent advent of the electron microscope. A short description of the instrument and the role it is beginning to play in virus research will be pointed out.

Furthermore, a brief review of the so-called pleuropneumonia group of microorganisms appears to be in place, since they seemingly represent a link, a form transitional between the viruses and bacteria as we now know them.

A. VIRUSES

It has been the good fortune of bacteriology to be called twice within a period of some 80 years to help in solving the most important question in biology concerning the very nature of life.

First, Pasteur refuted experimentally the theory of spontaneous generation of life from inanimate matter by showing that living cells could never appear spontaneously in organic media. They could only result from contamination of the media with microbes introduced from the outside world. Now bacteriology is confronted again with a fundamental problem pertaining to the origin of organized living structure.

¹ From the Laboratories of Bacteriology of The Mount Sinai Hospital, New York, N. Y. This paper embodies a lecture delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York City, December 22, 1943. Since the presentation was intended only as a review of recent investigative work on this vast and rapidly developing subject, full credit to many important contributors could not be adequately given. The bibliography of the studies mentioned, with the exception of personal unpublished observations will be found in the following sources: *Biological Abstracts* of the past 5 years; *Symposium on Virus and Rickettsial Diseases*, Harvard School of Public Health, June 12-June 17, 1939, Harvard University Press, Cambridge, Mass., 1940; Rivers, T. M., *Viruses and Virus Diseases*, Lane Medical Lectures, Stanford University Publication, University Series Medical Sciences, Vol. IV, 1939; Rivers, T. M., Stanley, W. M., et al., Members of the Rockefeller Institute for Medical Research, *Virus Diseases*, Ithaca, New York, Cornell University Press, 1943; van Rooyen, C. E. and Rhodes, A. I., *Virus Diseases of Man*, Oxford Medical Publication, London, Oxford University Press, Humphrey Milford, 1940; Schwartzman, Gregory, *Phenomenon of Local Tissue Reactivity*, New York, Paul B. Hoeber, Inc., 1937; Smith, K. M., *A Textbook of Plant Virus Diseases*, Philadelphia, P. Blakiston's and Son & Co., 1937.

On examining the long chain of evolutionary development of life from highly organized systems to simple forms it becomes suggestive that there may exist living units transitional between inanimate and living matter. Generally speaking, the viruses seem to occupy this intermediate position between the two worlds. As presently conceived, they may be structures so small as to escape observation with the optical microscope. Their life processes may be so slight as to elude detection by means of the biochemical and physiological methods thus far available. They may be so primitive in organization as to make them fully or in part dependent on a parasitic existence inside of the cells of a host more fully developed.

It would be erroneous to proceed any further in the characterization of these transitional forms of life or in the attempts to fit all known viruses into one broad group. Classification of this sort may only confuse and handicap future progress. As a matter of fact, the very properties which in the early days were considered as common features, on further analysis and with the aid of more refined methods now serve to differentiate one virus from another. It becomes obvious as the work progresses that there may be a number of groups of viruses different in their nature and properties. In view of this, the viruses must be defined merely by a description of their behavior, as follows:

I. Pathological Effects of Viruses

Since viruses cannot be seen their existence can be only detected by the pathological effects which they elicit in the susceptible host.

The lesions observed are *inflammatory, proliferative and degenerative*. I shall discuss them only to the extent necessary to indicate the difference between these lesions and those produced by bacterial agents.

In evaluating the virus lesions, the frequently supervening bacterial infections must be clearly differentiated from primary virus lesions. As early as 1874 Weigert asserted that the primary changes caused by the virus of small pox were non-inflammatory but necrobiotic in nature, the inflammatory changes appearing as a secondary phenomenon. It is widely accepted now, after much controversy, that the essential primary damage expresses itself in hyperplasia and degeneration of cells involved, as illustrated by a long list of virus diseases in which the development of lesions was studied in close detail; namely, in vaccinia lesions of rabbit's cornea, in lesions of molluscum contagiosum, in the epidermis infected with fowl pox, in the ganglion cells of rabies infection, in the nerve cells of monkeys with louping ill, etc. The sequence of events is best illustrated by two examples. Rivers observed at frequent intervals changes in the rabbit cornea infected with vaccinia. Three to 6 hours after inoculation hyperplasia of epithelial cells began to take place. The cells became larger, stained less intensely and showed mitotic figures and amitotic giant cells. Small nodules appearing on the surface of the cornea 24-48 hours after inoculation revealed hypertrophy and increase in the number of cells. Degeneration became manifest 48 hours after inoculation. Rivers also had the occasion to observe in detail the evolution of fowl pox lesions resulting from mosquito bites. Here again

There was no evidence of inflammation. The only changes were hyperplasia and formation of vesicles. Significantly there appeared inflammation only in tissues beneath the vesicles.

Similar hyperplastic changes were noted in many other virus diseases. They seem to be caused by multiplication of intracellular virus bodies. As studied by Woodpasture on the example of fowl pox, the hyperplasia may be so active as to resemble strands of carcinoma. The irritating effect of intracellular inclusions leads to prompt division of the cells. However, the division does not continue indefinitely. Soon there is observed division of nuclei, the cytoplasm failing to divide but becoming hypertrophied, vacuolated, and finally bursting to bring about release of the virus bodies.

In virus infections of greater severity, the immediate result is prompt lysis of the cells. The hyperplasia may either fail to occur, or being of a short duration, escape observation.

Furthermore, hyperplasia is absent in cells incapable of division as nerve cells infected with poliomyelitis, rabies and louping ill. In these diseases, therefore, there is observed only lysis of the cells.

In contrast, in some virus diseases the proliferative changes may be greatly enhanced, the lytic effects being of lesser significance. These viruses are obviously capable of stimulating production of neoplastic tissues closely resembling benign and malignant tumors — as illustrated by *chicken* tumors appearing as myxoma, fibroma, spindle-cell-sarcoma, chondroma, osteoma, round cell sarcoma; infectious papilloma of *dogs* and *cattle*; verruca vulgaris of *man*; *rabbit* papilloma, fibroma and Sanarelli's myxo-sarcoma; and finally condylomata of *man*.

Thus the primary virus lesions are essentially proliferative and degenerative. The inflammatory changes caused are seemingly due, however, to the supervening bacterial effects, or concerted effects of viruses and bacterial agents. A clear-cut illustration of the symbiosis is given by studies of Shope on swine influenza. Swine infected with a bacteria-free tissue extract containing the virus of influenza developed only a mild disease, in some instances so slight as to completely escape recognition. None of the animals exhibited a febrile reaction. Those coming to autopsy showed scattered areas of pulmonary atelectasis characteristic of the virus disease. On the other hand, when normal swine were inoculated with cultures of influenza suis bacilli, the findings were negative both clinically and at post mortem examinations.

When swine received mixtures of the virus and B. influenza suis they developed typical swine influenza. The malady was much severer than with the virus alone, and showed characteristic atelectasis variable in extent and distribution. In addition there was edema of lymph nodes, hyperemia of gastric mucosa and catarrhal exudation of the colon.

The striking modification of virus lesions by means of bacterial agents finds experimental illustration carried out prior and independently in connection with my studies on the phenomenon of local tissue reactivity to bacterial filtrates.

In the first publication on the phenomenon attention was drawn to the fact that skin sites made reactive by a local preparatory injection of a potent bacterial

filtrate may develop severe hemorrhagic and necrotic lesions following the intravenous injection of the same filtrate as well as of filtrates derived from unrelated bacteria, provided of course that each of the filtrates used was endowed with the necessary phenomenon-producing factors. Following this observation it was shown by Gratia that the necessary state of skin reactivity may be also elicited by intradermal injection of vaccinia virus, whereupon an intravenous injection of a potent bacterial filtrate may convert a mild vaccinal lesion erythematous in character into a severe hemorrhagic and necrotic site surrounded by extensive inflammation. The observations were later extended and confirmed in my laboratory in the investigations by Koplik. These experiments parallel clinical observations on cases of hemorrhagic forms of small pox which are almost invariably associated with streptococcus hemolyticus bacteremia.

II. Consideration of Pathogenesis of Virus Diseases in Reference to Selective Affinity for Susceptible Tissues; Susceptibility of Animal Species; and Routes of Invasion

In order to pursue the original plan of defining viruses by describing their properties and effects the outstanding feature of selective affinity of the viruses for organs of the susceptible host must be presented in some detail. The relationship so clearly characteristic of viruses is best illustrated by a large and clinically important group of diseases in which the etiological agents exert selective affinity of various degrees for the central nervous system. The time allowed will not permit any consideration of equally interesting facts concerning other groups of viruses namely those showing affinity for the upper respiratory tract, etc.

The virus diseases showing predilection for the central nervous system could be variously classified. It seems that the most suitable grouping which takes as a basis the organs predominantly affected is a somewhat modified classification originally suggested by Fothergill and summarized in Table I.

The encephalitides given in the table are primarily caused by the viruses. Another large group of encephalitides characterized chiefly by perivascular demyelination is omitted in view of the fact that in all probability they represent sequelae of diseases in which the etiological agents elicit *primary* lesions in organs other than the central nervous system, such as the encephalitides following vaccinia, measles, varicella, etc.

Thus, as may be seen from Table I, significant differences in tropism may be observed among viruses having primary predilection for the central nervous system.

Furthermore, when a given disease is studied in various animal species a wide range of response may be encountered. Some animal species may be totally refractory; their susceptibility may vary in degree; the pathological manifestations are not necessarily the same in all susceptible species, i.e., the strictness of tropism may show considerable fluctuations. In addition, the route of invasion of the viruses in the susceptible host may determine in an important manner the sites of localization and pathological manifestations.

The relationships shown in Table II serve usefully for identification and differentiation among viruses having many features in common.

A few remarks on some of the diseases may be of interest:

The monkey was the only animal in which typical poliomyelitis could be produced until 1939 when Armstrong reported interesting studies on the so-called Lansing strain. The brain from a fatal case of bulbar poliomyelitis was first transmitted by seven serial passages through a newly tested rodent, the Southern cotton rat. Each passage gave typical flaccid paralysis in monkeys. When the 14th rat passage was injected into mice, a typical picture of poliomyelitis was elicited. Since then the Lansing strain has been widely used without fail by many investigators. The mouse strain is always able to produce typical poliomyelitis in the monkey and it is neutralized by sera from convalescent human cases and from convalescent monkeys. Thus the identity of the Lansing strain with human and monkey poliomyelitis strains is beyond question.

TABLE I
ENCEPHALITIDES

a. Nerve cells involved			b. Viscerotropic reaction mainly meningeal	c. Mainly vascular
Strictly neurotropic	Pantropic			
Poliomyelitis	Relatively more neurotropic	More widespread pantropism	Vaccinia	Fox encephalitis
Rabies		Many insect transmitted	Lymphogranuloma inguinale	Hog cholera
Borna disease	Herpes B. virus		Salivary gland disease of guinea pigs	
Pseudorabies (in the monkey)	Pseudorabies (in the rabbit)	Equine encephalomyelitis	Mumps	
	St. Louis	Yellow fever	Lymphocytic chorio-meningitis	
	Australian	Louping ill		
	Virus III	Japanese B		
		Vesicular stomatitis		
		? Dog distemper		

The possibility of producing the disease in mice² is of great value, and will facilitate progress especially now when the African monkeys are very difficult to obtain. Subsequently to Armstrong's publication other claims on similar adaptations were made which could not be equally well substantiated since the strains adapted produced no pathogenic effect when returned to monkeys and the results of neutralization reactions were somewhat ambiguous. About a month ago Olitski reported that he was able to elicit the disease in rats and mice with a human strain from the Middle East. This claim is fully supported by the necessary tests.

The history of the investigations on the epidemic of encephalitis in St. Louis is

² Readers interested in this aspect of studies on poliomyelitis are referred to recent papers on Theiler's disease in mice, by Theiler, Gard, Olitsky and others.

well-known. The virus strains recovered in the epidemic elicited the typical malady in mice and monkeys. Pathologically and clinically the disease appeared closely related to the Japanese encephalitis, Type B. Webster and others clearly differentiated the two viruses by their effect upon various animal species already described and by the fact that no cross protection was afforded specific antisera.

TABLE II

Some examples of susceptibility of animals to virus diseases of the central nervous system

	ACUTE ANTERIOR POLIOMYELITIS	ASCENDING MYELITIS B	ENCEPHALITIDES			
			St. Louis	Japanese	Australian X	Herpes
Animals strongly suscep- tible	Monkeys, (rhesus, chimpanzee); cotton tail rats and mice some strains of virus	Rabbits; monkeys (rhesus and cebus); guinea pigs	Mice	Mice; guinea pigs; rab- bits; rhe- sus mon- keys; sheep	Mon- keys; sheep; horses; calves	Rabbits; guinea pigs; mice
Animals of mod- erate or ques- tionable suscep- tibility	New world monkeys		Rhesus monkeys	White rats (ques- tionable)		Rats; dogs; birds; America callithrix (titi) monkeys
Refractory animals	American mon- keys (spider and marmo- set) and all other labora- tory animals	Mice	Cebus mon- key; rab- bits; guinea pigs; rats; sheep; cats; ferrets	Dogs; cats; chicken; cotton tail rats; goats	Dogs; cats; rab- bits; guinea pigs	Rhesus monkeys
Animals with natural diseases		Monkeys			Cattle; sheep	

Following this work a virus of encephalitis was recovered from fatal human cases which occurred in the Russian spring epidemic of 1938. Interestingly the Russian virus similarly to the Japanese B virus was insect-borne. However, there was a difference in the species of the insect carrier, in the Russian epidemic tick being the transmitter and in the Japanese, the mosquito. There was also observed an immunological relationship between the two viruses. Animals immunized with the Russian virus were also immune to the Japanese virus. How-

er, animals immunized with the Japanese virus were only incompletely protected against the Russian virus. This fact indicated that the two antigens were related, the Japanese virus being less complex than the Russian virus. On the other hand, the Russian virus is also closely related to the louping-ill of Scotland which in turn is related to the Australian X disease.

Now, epidemiologically these findings are very interesting since together with the supporting evidence they suggest the following facts:

The louping ill occurred among sheep and men in 1914 in Scotland from where it apparently reached Australia in the form of Australian X disease also of sheep and man in 1917, and from there in the early thirties it seemed to have spread to Japan under Japanese B virus. From Japan the virus may have traveled through the Pacific to settle in St. Louis in 1934, and also from Japan to Russia in 1938. If those epidemiological data are granted, the fact is brought out that the mode of transmission and the species of insect-carriers was changed as the virus traveled around the globe. The change of intermediate host apparently was responsible for the slow progress of epidemics and variations in the disease-manifestations. Other examples of possibly similar epidemiological variants of a disease entity may be the European Borna disease of horses, the American Eastern equine encephalomyelitis and American Western encephalomyelitis which are all insect-borne, pathogenic to man, and related immunologically; the differentiation among strains being mainly based on differences in susceptibility of various animals species.

Mention cannot be omitted of another group of interrelated viruses having viscerotropic properties, i.e. the lymphocytic choriomeningitis proper; the pseudo-choriomeningitis; the *maladie des porchers* of Switzerland (the malady of swineherds) and Durand's disease.

The lymphocytic choriomeningitis proper produces experimentally fatal and typical disease in mice and guinea-pigs, and occurs as a natural disease of these animals and man. The pseudo-choriomeningitis found in man is distinguished from the lymphocytic choriomeningitis proper serologically and by the fact that it gives a milder disease in mice. The malady occurs among swine causing incidentally to meningitis a typical torsion of the head to one side; producing in man meningoencephalitis with maculo-papular eruption of the skin. Finally the Durand disease of similar clinical syndrome of meningitis is differentiated from the lymphocytic choriomeningitis by the refractoriness of mice and guinea-pigs; while in contrast to lymphocytic choriomeningitis, rats, ferrets and cats are susceptible to the disease.

Help in differential diagnosis is not the only benefit derived from the relationships indicated. When considered together with the pathways of invasion and the distribution of the viruses in the body of the infected animal, information may be also gained on the pathogenesis of certain diseases.

The accepted definition of strict neurotropism implies that the virus grows and multiplies along nerve trunks. No evidence of these viruses is found in the blood. The classical example of this group is the acute anterior poliomyelitis. For a while the belief arose that there existed a single pathway of invasion of the

virus. On the basis of experimental evidence in monkeys, the conclusion was drawn that the sole portal of entry was the olfactory portion of the nasal mucosa. From this area the virus was believed to spread along the olfactory nerves to the olfactory bulbs and from there along the olfactory tracts to the central nervous system. This assumption was supported by the fact that the disease could be elicited by intranasal instillation of the virus and it failed to occur when prior to the instillation there was induced degeneration of the olfactory nerves. In the light of the present information, however, the nasal mucosa cannot be considered the only route of invasion in a natural disease. The erroneous belief was due to the attempted generalization granting that the pathogenesis demonstrated for monkey was necessarily the same in man:

Assuming that in a strictly neurotropic disease of this sort the invasion is initiated at the nerve endings, the olfactory nerve endings well-exposed to the exterior obviously may offer an easily accessible site for invasion. It was shown, however, that this route was not the only one available. On examination of human material no consistent evidence was found of any inflammatory reaction in the olfactory nerves and tracts which would indicate the passage of the virus. No virus was detected in the olfactory bulbs. Furthermore, evidence is accumulating that the pharyngeal and intestinal mucosa may be by far the more important avenues of invasion. The virus is frequently demonstrable in stools, rectal washings of patients and in the sewage of epidemic districts. It is now believed that while the nasal mucosa may be a significant portal of entry in experimental poliomyelitis of the monkey, the routes of invasion are quite different in man.

Observations indicating the importance of individual consideration of host susceptibility and predisposition in the evaluation of facts concerning pathogenesis are further amplified by the experiments with pantropic viruses. The latter viruses may attack the central nervous system as well as cells of other embryonic origin. Neurotropism is only one manifestation. In addition the viruses cause focal necrosis in various organs.

The characteristic feature of pathogenesis of pantropic viruses is in the finding of the agents in the blood stream. The examples most studied are the Western and Eastern types of equine encephalomyelitis. The disease deserves serious consideration in view of its comparatively recent discovery as a natural disease of man. In this disease different pathways may be operative in various animal hosts. Sabin and Olitski have found that in mice the virus may spread from the muscle, as the initial portal of entry, to the central nervous system, by way of the peripheral nerves; or from the same initial site by way of the blood stream to the nasal mucosa, and from there by way of the olfactory nerves to the central nervous system. Thus, the blood stream participates in the transfer of the virus in both animal hosts. In the mouse it is brought to the central nervous system by way of peripheral nerves. In the guinea-pig it is transported directly into the central nervous system apparently through the meningeal barrier. These studies were further elaborated by observations on the relation of age of the animals to susceptibility to infection.

was shown that resistance to the malady was much greater in adult than young mice. The blood of young mice contained a large amount of virus, while no virus could be detected in the blood of adult mice following intraperitoneal inoculation of large doses. In contrast, equal susceptibility to the disease was observed in all age groups following intracerebral inoculation of the virus.

As just seen and as it may be also seen from similar observations on other zoonotic viruses not quoted here, the blood stream participates in a significant manner in the transfer of viruses from the initial point of invasion to the site of predilection. However, the mode of the transfer of the viruses through the blood still remains a subject for investigation. It is obvious that the transfer must be governed by some regulating mechanism. Indeed, in the absence of such regulation viruses entering the blood stream could be expected to attain promptly a state of considerable dispersion, a fact which would make difficult to understand how the sites of predilection can be reached with the unfailing regularity observed under suitable conditions.

In order to investigate this problem I made the assumption that a virus may anchor itself on some constituents or cells of the blood which by virtue of their physiological function are destined to come into intimate contact with the site for which the virus has a selective affinity. The example selected for the studies was the virus of lymphocytic choriomeningitis. The strains available for the study differed from one another in their virulence for guinea-pigs and mice. Two strains possessed high virulence for the guinea-pig and a moderate virulence for the mouse. One strain was of high virulence for the mouse and was of moderate virulence for the guinea-pig. The fourth strain was of low virulence for both animal species. The differences in virulence mentioned found a clear expression in the clinical picture elicited. Thus, in the guinea-pig high virulence implied a short severe course which was accompanied by a high rise in temperature promptly followed by a sharp drop to a subnormal level. Death occurred during the latter afebrile period. There was general weakness, prostration, marked loss of weight and other signs of generalized infection; meningitis and symptoms of cerebral irritation, i.e. tremors, convulsions and tonic extensions of hind legs. Moderate virulence was expressed by a protracted illness with frequent survivals, lower fever and absence of temperature crisis. Similar observations were made on mice except no temperature record was obtained.

In my investigations on these strains it was shown that the virus could be found in association with erythrocytes of infected guinea-pigs and mice. Various strains of the virus differed from one another in their affinity for the erythrocytes of these animals. When a strain showed a decidedly greater virulence for one species than another, there was observed consistent infectivity of erythrocytes of the species for which the strain possessed the greater virulence. The virus could be recovered only irregularly from erythrocytes of mice and guinea-pigs when the infecting strain showed low virulence for both species.

Now, the point of interest is that association of the virus with the erythrocytes paralleled the ability of the strain to elicit a disease of severe type. It is

suggestive, therefore, that the transfer of the virus through the blood by means of erythrocytes may prove to be a factor of importance in determining the course of the disease, and possibly its dissemination and generalization. In this connection the observations of Smadel and Wall are of interest. The authors found that the concentration of the virus in the spleen was greater when the infection was severe. In view of my observations just mentioned it is possible that the virus is transferred to the spleen by the erythrocytes. This assumption is supported by my findings that the virus associated with erythrocytes is best liberated by hemolysis, a process of physiological occurrence in the spleen. It remains to determine the fate of the virus thus brought in contact with the portal circulation and the liver. Incidentally, to this topic the most interesting previous work of Hirst must be mentioned. He found that the virus of influenza produce *in vitro* agglutination of red blood cells of a number of animal species. The observations are important because they give an *in vitro* test for detection of the influenza virus.

TABLE III

Infectivity of erythrocytes from mice and guinea pigs inoculated with various strains of Lymphocytic Choriomeningitis Virus

STRAIN	ANIMAL SPECIES	VIRULENCE	INFECTIVITY OF ERYTHROCYTES
W. E.....	Guinea pig	High	Consistent
W. E.....	Mouse	Moderate	Absent or irregular
F. A.....	Guinea pig	High	Consistent
F. A.....	Mouse	Moderate	Absent
W. W. S.....	Guinea pig	Low	Absent or irregular
W. W. S.....	Mouse	High	Consistent
T.....	Guinea pig	Low	Absent or irregular
T.....	Mouse	Low	Absent or irregular

enza virus. No studies on association of the influenza virus with the erythrocytes of the infected animal have been thus far reported.

III. Parasitism and Morphology of Viruses

Another important characteristic feature of viruses is extreme parasitism.

a. *Cultivation.* Most of the members of viruses can only grow and multiply *in vivo* in the cells of the susceptible host. Thus far no cultures in artificial media could be obtained, although considerable progress was achieved by *in vitro* cultivation of viruses in explanted tissue cultures and in chick embryos. Since these studies have only experimental value they will not be presented in detail.

b. *Intracellular inclusions.* Another manifestation of extreme parasitism is that the viruses may be found intracellularly in the form of so-called intracellular inclusions. Some examples are given in Table IV.

Additional remarks may serve to characterize their morphology. Thus,

Henderson-Paterson bodies of the molluscum contagiosum are large eosinophilic inclusions. The inclusions of this type may vary from 5-20 μ in diameter, are spherical in shape, also may be elongated or triangular, homogenous or granular. The small eosinophilic inclusions are simply smaller forms of the large ones.

TABLE IV
Virus intracellular inclusions

Name of inclusions and disease	INTRACYTOPLASMIC INCLUSIONS				INTRANUCLEAR INCLUSIONS		
	Eosinophilic		Basophilic		Trachoma type	Type A	Type B
	Large	Small	Large	Small			
	*Guarneri bodies of variola-vaccinia	Early forms of large eosinophilic inclusions	Rarely formed and not characteristic of virus infections	Bodies of encephalitis lethargica (?)	*Trachoma	Lipschütz bodies of *herpes zoster and febrilis	Poliomyelitis (?)
	*Negri bodies of rabies			Herpes febrilis (?);	*Inclusion conjunctivitis		*Rift valley fever
*Henderson-Paterson bodies of molluscum contagiosum	*Lympho-granuloma inguinale			*Psittacosis		*Borna disease	
Marshall bodies of mouse ectromelia					Yellow fever		
Guarneri-like bodies in encephalitis Japanese B (?)						*Virus III infection of rabbits	
					Fox encephalitis	Nicolau bodies of herpes zoster febrilis	
					*Louping ill		
					*Pseudo-rabies		
*Bollinger bodies of fowl pox							

* = Inclusion bodies of clearly established specificity
(?) The significance of these bodies is undecided

Negri bodies, an example of eosinophilic inclusions, are best shown in the cytoplasm of nerve cells from the hippocampus major of a dog suffering from hydrophobia.

Guarneri bodies are also eosinophilic; they occur in the cytoplasm of the

corneal epithelial cells and may be seen in the disease of the rabbit, when homogeneous and granular bodies are surrounded by an unstained halo.

The intracytoplasmic basophilic inclusions are illustrated by very interesting examples of psittacosis and lymphogranuloma venereum as demonstrated by Bedson in the large mononuclear cells of the spleen. The inclusions are clearly shown by him to represent various developmental cycles, the development consisting of gradual transformation from homogeneous masses into minute elementary bodies. In greater detail the growth phases may be described, as follows:

First phase is the stage of plasmodium-like forms, or plaques in the cells seen six hours after inoculation of the virus. Next, within 48-72 hours after inoculation the morulas begin to differentiate into elementary bodies. The cells themselves break up and the elementary bodies are freed.

A little later it is possible to observe fragments of the plasmodium-like forms of the morula and many free elementary bodies which may be about 0.25 μ in diameter, while the plaques are as large as 1 μ . The large forms are less infective than the small ones and appear to be the resting stages.

Basophilic intracytoplasmic inclusions are well illustrated by granulocytuscles of lymphogranuloma venereum. They may be seen singly or in pairs in histiocytes from meninges.

To the third group of inclusions belong the trachoma-like bodies. Their characteristic feature is in the variable staining affinities: 1. In the *early stages* of development there are seen basophilic forms, i.e. slender filaments, filaments of dumb bell appearance and also a number of small elementary bodies. 2. The *later stage* shows a change to acidophilic forms, with increase in size, and the presence of diplococcus forms. 3. Finally there appear the *mature forms* embedded blue staining plastin-like material.

In the inclusion-conjunctivitis, there may be observed a mass of elementary bodies adjacent to the cell nucleus.

The remaining inclusions are intranuclear, which are divided into two sub-groups:

The first sub-group consists of amorphous or granular deposits in the nuclei which themselves become disrupted. The nuclear margin is characteristically well-defined due apparently to collection or displacement of basichromatin. The surrounding tissue as a rule shows severe reaction.

The second sub-group is distinguished by absence of nuclear margination, circumscribed appearance of inclusions and the fact that reaction in the surrounding tissues is less intense than above.

A word should be said about the specificity of intracellular inclusions, a question debated for many years. It seems that a clear idea has been now gained on criteria necessary for determining their relation to viruses. The general consensus of opinion is that the intracytoplasmic inclusions in many instances may be considered identical or closely related to the viruses themselves. This belief is based on the characteristic morphology invariably associated with the respective viruses; the fact that their presence can be accurately correlated with the infectivity of the tissues and finally, the most important proof rests on

the observation that the forms may be produced in chick embryos infected with the viruses. On the other hand, there are many intranuclear inclusions which may be taken as having a dubious relation to the viruses. Intranuclear inclusions, as a rule, need a more careful study before one is permitted to claim their association or identity with a virus. There are, however, criteria of help, which are based on the fact that in true intranuclear inclusions it is possible to demonstrate by the use of the methods of Feulgen and McCallum absence of deoxyribonucleic acid and masked iron, respectively. In contrast, in bodies resulting from nucleus degeneration both tests are positive, thus confirming the nuclear origin. Also, intranuclear inclusions sometimes resulting from digestion of leucocytes can be differentiated from virus inclusions by an oxidase reaction positive for leucocytes. Thus, certain tests make possible to differentiate the true from the false intranuclear inclusions seen in non-infected tissues injected with foreign bodies.

The inclusions reviewed represent probably the most tangible information thus far available on the morphology of viruses. In addition, however, by somewhat indirect physico-chemical methods valuable and accurate knowledge was gained on the diameter of the virus particles.

c. Physico-chemical methods for study of size of particles. The scope of this presentation permits only a brief mention of the following methods, which are of purely experimental interest.

The ultrafiltration through collodion membranes of graded porosity developed recently by Elford gave a fairly good estimation of the diameter of particles filtered. The velocity of sedimentation of particles in the air-driven ultracentrifuge of Svedberg at known gravitational force of the centrifugal field can be determined by optical recordings. From these data, by means of Svedberg's equation, the size of the particles can be derived assuming that the shape of the particle is spherical or nearly spherical. Finally the newer methods of electrophoreses of Tiselius in which the migration boundary is recorded optically, may be also successfully used for determination of the diameter of particles. The results are given in the illustration of Plate I.

d. Electron microscopy. I have delayed thus far mentioning electron microscopy because the method only assumes importance when considered in its proper relation to the knowledge on viruses acquired by other means.

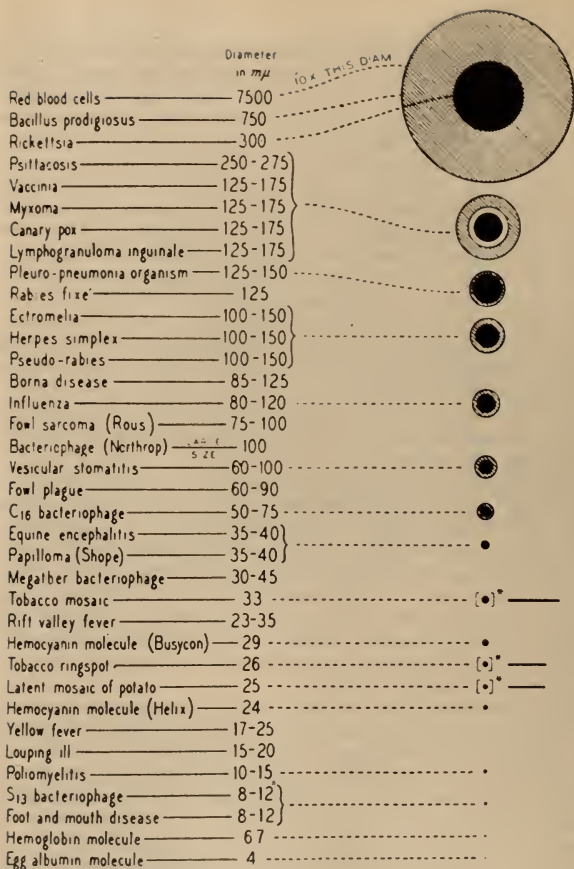
The description of the electron microscope itself is difficult without a demonstration of the instrument, although a brief discussion of the principle on which its construction is based may be in place.

Electrons are some one hundred times shorter and faster than the shortest light wave. Obviously, then when utilized for visualization of an object, respectively greater magnification is theoretically obtainable.

The utilization of the electrons for microscopy is made possible by the following:

Although electrons are by themselves invisible, they may be seen when made to fall upon a fluorescent screen or are made to record the image on a photographic plate.

Since the penetrating power of the electrons is low, they are scattered by



* Known to be very asymmetrical

PLATE I
COMPARATIVE SIZES OF VIRUSES*

* Reproduced by permission of Dr. Stanley from "Virus Diseases," T. M. Rivers, W. M. Stanley, et al., Members of the Rockefeller Institute for Medical Research, Ithaca, New York, Cornell University Press, 1943. The column indicating the molecular weights was omitted.

objects encountered in their pathway. The extent of scattering depends on the so-called "mass thickness" of the object. Since the mass thickness is equal by definition to density multiplied by irradiated thickness, the greater the mass thickness the darker the image. If the thickness of the objects examined is kept approximately constant, the darkness of the image becomes a measure of density of the object. In describing an electron image it is more accurate, therefore, to speak of degree of density than of the degree of darkness.

An electromagnetic field acts upon a beam of electrons in the same manner as a glass lens acts upon a beam of light. It is possible, therefore, to arrange a system of electromagnetic fields which take the place of the condenser, objective and eyepiece of the light microscope, thus focussing the electrons sharply upon the object and then projecting its image for direct examination and photography.

Although lower than may be expected from theoretical calculations, the magnification with the electron microscope attained is indeed great. Of even more significant advantage is the high resolving power of the instrument. The limit being about 50 \AA. , the resolving power of the electron microscope exceeds that of the light microscope by some 80-90 times.

Although magnification as high as 20,000 times is usually obtainable, the convenient magnification permitting sharp focussing and good light intensity is ordinarily 10,000 diameters. At this magnification bodies with a diameter of $10 \text{ m}\mu$ form an image with a diameter of 0.1 mm. Since, as already seen, the diameter of the majority of viruses exceeds $10 \text{ m}\mu$, the magnification of 10,000 diameters proves quite satisfactory for research on unknown disease agents.

It may be stated, however, that in spite of the fact that the dimensions of the viruses fall well within the range of the resolving and magnifying powers of the instrument the progress has not been as rapid as anticipated. The main reason is due to the necessity to use suspensions of infected tissues for the search of the viruses. Obviously the search is handicapped by the presence of contaminating debris of the tissues.

Thus far reports have been made on the electron microscopy of a limited number of viruses, namely, vaccinia virus, virus of Shope papilloma, equine encephalomyelitis and influenza by Rivers, Smadel, Anderson, Rivers, Beard, Chambers et al. The viruses investigated were purified by chemical means, ultracentrifugalization and filtration. In these studies the vaccinia virus showed some distinctive characteristics. The work of Beard and his associates is of doubtful value, in view of the fact that the author found it necessary to add calcium chloride to this preparations. The effect of the salt on the images seen awaits further clarification. Furthermore, most of the viruses observed appeared as oval or round bodies. In the absence of any distinguishing characteristics difficulties were experienced in differentiating these bodies from particles of similar shape also seen in control tissue extracts. The proof that the bodies seen were those of the viruses themselves rested on the fact that their dimensions approximated the values derived from ultrafiltration and sedimentation constant determinations.

In my studies the virus of lymphocytic choriomeningitis was selected for

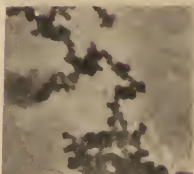
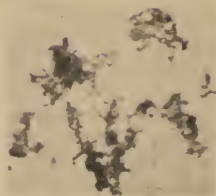
**1A****1B****2****3A****3B**

PLATE II

THE ELECTRON MICROSCOPY OF THE VIRUS OF LYMPHOCYTIC CHORIOMENINGITIS

1A and 1B: Contact prints of complex "giant" forms in a preparation of Guinea-pig brain infected with W.E. strain of lymphocytic choriomeningitis. Eluate II.

1A: Magnification 1 micron = 1.5 cm. This form consists of 3 parts: an oval head of high density; a mid-portion; and a tapering process.

1B: Magnification 1 micron = 1.35 cm. Another type of a "giant" form consisting of 2 portions only. No tapering process seen.

Observations on these individual forms aided in the recognition of the virus bodies in concentrated preparations, as shown in the following photograph 2.

2: Contact print. Eluate I of preparation of Guinea-pig brain infected with W.E. strain of lymphocytic choriomeningitis. Magnification 1 micron = 1.35 cm.

observations. The virus is very labile. A method of purification was sought which would be likely to cause little damage to the virus. These attempts are greatly helped by an incidental observation, that the virus of lymphocytic choriomeningitis adheres strongly to glass surfaces. The following method of purification was then developed:

Brains of animals infected with the lymphocytic choriomeningitis virus were suspended in Locke solution, and centrifuged lightly to remove gross particles. The supernate was further diluted in Locke and then added to a small tube into which there were previously placed 25–30 fine capillaries this was. Obviously done in order to obtain a large glass surface. After a short contact with the capillaries the fluid was removed and discarded. The tube with the capillaries was then filled with sterile Locke solution and left in contact for $\frac{1}{2}$ hour at 4° C. The fluid removed represented eluate I. The washing of the capillaries was then similarly continued to obtain eluates II and III.

The eluate I contained some contaminating material. Eluates II and III, were buiret negative, proved highly infectious to experimental animals and on electron microscopic examination showed little or no contamination. They contained, however, bodies of well-defined and characteristic morphology. Two forms were observed. The first form was an elliptical body of high density. The second form was also an elliptical body of high density to which there was attached a long filament. In addition some giant forms were observed. These forms are illustrated in Plate II, illustrations 1A, 1B and 2 and the dimensions are indicated in the respective legends.

The recognition of the bodies described in connection with lymphocytic choriomeningitis is based on a long series of observations which is briefly as follows:

Similar preparations of control brains of mice and guinea-pigs failed to reveal the structures. All eluates which showed clearly defined and undamaged forms elicited on intracerebral injection typical lymphocytic choriomeningitis in mice and guinea-pigs. Immune antiserum gave specific protection. The bodies were seen in brains from mice and guinea-pigs infected with 4 strains of the virus in an approximate total of 100 preparations.

Addition of immune guinea-pig antiserum and human convalescent serum to the virus of infected mouse and guinea-pig brains resulted in formation of long branching chains in which the bodies described could be identified by the presence of the "heads" of high density. The aggregation is shown in Plate II, illustrations 3A and 3B.

PLATE II—*Continued*

Note some contaminating material usually found in Eluate I. The complex virus bodies varying in size with heads of high density may be clearly distinguished.

3A: Contact print. Eluate II of mixture of Guinea-pig brain infected with W.E. strain with equal amount of Guinea-pig immune anti-serum in final dilution 1:64, incubated at 10 C for $\frac{1}{2}$ hour and room temperature for 1 $\frac{1}{2}$ hours. Magnification 1 micron = 1.35 cm.

3B: Contact print. Eluate II of a mixture of Guinea-pig brain infected with W.E. strain with equal amount of Guinea-pig immune anti-serum in final dilution 1:128. Magnification 1 micron = 1.35 cm.

3A and 3B: Note branching chains of clumps in which the virus bodies may be identified by oval heads of high density.

Normal sera failed to produce this effect. Numerous specimens of preparations made by the use of other methods revealed only occasionally the form described.

Recently an opportunity was afforded to see the bodies in eluates of supernatant of lightly centrifuged spinal fluid obtained from a case of lymphocytic choriomeningitis in this hospital. The virus was demonstrated in the same specimen by intracerebral inoculation of mice and guinea-pigs. Aggregates similar to those described above were obtained on addition of anti-lymphocytic choriomeningitis guinea-pig serum to the spinal fluid.

Thus eluates of the virus adsorbed on glass surfaces exposed to contact with infected brain suspensions and the spinal fluid from the human case showed the presence of bodies of considerable complexity and marked difference in size. They could be, however, easily identified by characteristic morphology. The fact that immune guinea-pig anti-lymphocytic choriomeningitis serum and human convalescent serum caused aggregation of the bodies obtained from human spinal fluid and infected mouse and guinea-pig brains suggests that the bodies described may be closely related to the virus of lymphocytic choriomeningitis.

B. PLEUROPNEUMONIA-LIKE MICROORGANISMS

As already mentioned, our conception of the nature of viruses may be greatly helped by examination of the so-called pleuropneumonia-like microorganisms. The term is really very inadequate. It must be, however, used because the microorganism cannot be adequately classified with any known forms whether belonging to the true or higher bacteria. It remains to define the pleuropneumonia-like microorganism by the following characteristics:

First the microorganism may be singled out by its extreme pleomorphism, resulting from the existence of various phases of cyclic development. The forms seen range widely in their dimensions. In the phase of elementary bodies, the organism may have a diameter as small as 125-150 m μ . In this magnitude it is capable to pass through a porcelain filter and be hardly seen or not at all under the light microscope. The larger forms, on the other hand, may be as large as true bacteria, and surprisingly, even much larger approximating the dimensions of higher bacteria.

The second important differentiation from bacteria is based on the fact that there exist two alternative modes of multiplications, namely (a) simple division and (b) the sexual mode of reproduction similar to the development of protozoa.

Thirdly, the microorganism exhibits pronounced ameboid tendency to change quickly its shape, a property unknown among bacteria. This process brings about formation of protozoan-like bodies.

Finally, at certain stages of development, the bodies may become highly parasitic, and capable of leading an intracellular existence in the susceptible host.

From this enumeration of the main features it becomes obvious at once that in certain phases the microorganism is closely related to viruses by being filterable; invisible under of the light microscope; and parasitic for the cells

the host. However, in other stages this microorganism bears all the characteristics of a true bacterium or even of a higher bacterium capable of growth in artificial media. And then, again in some forms it approaches protozoa in form and mode of reproduction. Indeed, the pleuropneumonia-like microorganism may be broadly considered as a connecting link between viruses,



PLATE III

SCHEMATIC DIAGRAM OF DEVELOPMENTAL CYCLES OF PLEUROPNEUMONIA AND PLEUROPNEUMONIA-LIKE ORGANISMS*

- S_1 = monopolar spheroid
 S_{1-2} = bipolar spheroid
 S_2 = multipolar spheroid
 S_{2-3} = aggregates of spheroids. A sphere with polar bodies moving away.
 S_3 = transition to a filamentous stage
 F_1 - F_2 = filamentous and mycelium stages
 F_3 = stage of branching of the filaments
 E = resting stage

* Adopted from "Principles of Bacteriology and Immunity," W. W. C. Topley and G. S. Wilson, 2nd edition, William Wood & Co., 1937, with modifications.

bacteria and protozoa. A brief description of the morphology and a summary of the clinico-pathological significance of the microorganism are now in place. The developmental cycles are presented schematically in Plate III.

As may be seen in the first so-called resting or granular stage, the elementary bodies are predominant. There may be found granules as small as $115\text{ m}\mu$ in diameter, as well as rings and some small diplococci.

With proliferation of the resting organisms the rings transform into spheroids which begin to bud while the spheroids become distinctly spherical. The budding is responsible for the formation of monopolar, bipolar and multipolar spheres. The filamentous stage is reached when the buds move gradually away from the spheres. In many instances the spheres later detach from the filaments. The filamentous stage enters then the phase of ramification. Further increase in the number of filaments gives rise to mycelium-like structures. The protoplasmic condensations in the filaments of mycelium are quite frequent. Finally the phase of disintegration is reached, when the filaments break up and resting forms become again apparent. This complete cycle may be short-circuited (see arrow of the illustration).

The information concerning the pathogenicity of the microorganism is best presented in chronological order, as follows:

The pleuropneumonia proper microorganism was first discovered as the cause of a severe disease in cattle under the same name by Nocard and Roux in 1898. The extraordinary morphology was described in 1910 simultaneously by Bordet and by Borrel.

The clinical and pathological manifestations of the cattle disease consist of exudative inflammation of interlobular lymph vessels and alveolar tissue with serofibrinous pleurisy. In calves there is also conspicuous joint involvement with exudation.

A strain of similar morphology causes a disease in sheep under the name of agalactia. Joints and eyes of sheep are markedly involved. The mammary glands of lactating sheep are intensely inflamed. In mules the same strain produces a malady more systemic in nature. The lesions are arthritis, and vesiculo-pustular skin eruptions.

Public Health measures greatly reduced the incidence of the natural disease of sheep and cattle. The use of the organism for experimental work was forbidden by law in fear of spread. In view of this little work was done until recently with this most interesting microorganism.

However, in 1934, Klienenberg found this microorganism in symbiosis with another microbe of normal occurrence in rats, the *Streptobacillus moniliformis*. It must be emphasized that the streptobacillus moniliformis responsible for rat-bite fever is apparently not related to the pleuropneumonia-like microorganism. The association is seemingly only an accidental symbiosis. Following the work of Klienenberg, two more rat strains were isolated. The three rat strains are serologically unrelated to each other and to pleuropneumonia of cattle and agalactia. The strains are known under symbols L₁, L₃ and L₄. The L₁ and L₃ strains are non-pathogenic. Strain L₄, however, causes spontaneous polyarthritis in rats with edema, hemorrhage and necrosis of the joints.

At a later date Findlay in England and Sabin in America isolated some five mouse strains. Serologically they are to some extent related to each other, their pathological effects, however, are quite varied. The type A strain gave in the hands of Sabin most interesting pathological manifestations which unfortunately could not be duplicated, seemingly for loss of virulence, neither later by Sabin himself nor by other investigators. In the original observa-

ons the microorganism caused on intracerebral injection destruction of periventricular substance. When a toxin, free of the microorganism as injected, chorea developed similar to one observed in rheumatic children. On intravenous injection there was produced polyarthritis which was limited to periarticular connective tissue and synovia. No ankylosis and no cartilage involvement was seen. On the contrary, the type B strain gave no involvement of the central nervous system, eliciting only proliferative joint changes. The microorganism affected synovia, capsule and perichondrium, producing obliteration of joint cavity and replacement of chondrioblasts and osteoblasts by fibroblasts. In five months following inoculation there was complete ankylosis. With other three mouse strains arthritic lesions were also produced, similar to those obtained with the strain B.

Two strains from dogs, one from guinea-pig and several from London sewage were also recently recovered.

Obviously the most important problem still remaining is whether the organism plays any rôle in man. Thus far Dienes succeeded in obtaining 2 strains from female genitalia infected with gonorrhea.

A short time ago we were fortunate in our laboratory to obtain the microorganism from the blood of a patient. The bacteriological and clinical features of this microorganism will be soon described in greater detail by Miss Herschberger, Dr. Dantes and the author of this lecture. A brief mention may be, however, made here. Unfortunately no autopsy permission was secured. The clinical features were typical for subacute bacterial endocarditis. The patient was a white male of 24 with a history of a cardiac murmur developed at the age of 6. About a year before admission until the day of death gum bleeding was a conspicuous symptom. In the hospital, according to Drs. Libman and Dantes, manifestations were white-centered petechiae, loud heart murmur over precordium, more marked over the apex, spleen enlargement, irregular fever, clubbed fingers, edema of lower extremities, and red blood cells in the urine. Two positive blood cultures were obtained with countless colonies. Obviously the microorganism was present in the blood of the patient for a long period of time since a strong precipitation reaction was obtained with the patient's serum against an antigen prepared from the microorganism. The identification was made certain by a long series of cultural, biological and serological studies too technical for description.

Thus it seems that the finding represents the first instance of isolation of the pleuropneumonia-like microorganism from the human blood. The microorganism was apparently responsible for a fatal subacute endocarditis in a patient with a previous history of rheumatic heart disease. In view of the fact that the pleuropneumonia-like organisms are capable of producing in animals clinically interesting syndromes further attempts to determine their role in human pathology are highly desirable. The possible human pathogenicity is suggested by the observation in the case just described. The technical difficulty of isolation of the microorganism from human material may be further aided by the electron microscope. These studies are under progress.

I have imposed upon your attention for a long time because the problems are

vast and related to many fields of biology and medicine. I realize that I failed, however, to make any actual statement on the nature of the viruses. The failure is due to the belief shared by many investigators that under the general term of viruses there are presently gathered agents which may be widely different in nature.

Stanley succeeded in showing that crystallizable nucleoproteins are capable of causing virus plant diseases. Similar attempts failed, however, with mammalian viruses. Some etiological agents previously grouped as viruses were gradually taken off the list and described under bacteria; the pleuropneumonia-like organisms cause diseases resembling virus infections.

With the advent of new tools and methods information is being continuously gathered. The definition of the nature of the viruses remains, however, reserved for the future.

ULCERATIVE COLITIS¹

ASHER WINKELSTEIN, M.D.

In the brief time allotted, I will endeavor to throw some light chiefly on the disputed aspects of this remarkable disease in order to ascertain what progress has been made in recent years. The subject will be discussed under the following headings: (a) incidence; (b) etiology; (c) pathology; (d) clinical features; (e) medical therapy; (f) surgical therapy.

Incidence. A few words about the changing incidence of this disease. When I graduated as a medical student in 1917, I had seen only one case. It was only briefly described at that time in Osler's textbook of medicine. It was, however, well known to the Continental writers who called it "colitis gravis." Today we see in the wards of The Mount Sinai Hospital approximately 150 cases yearly. Typhoid fever has largely disappeared and ulcerative colitis has taken its place as the enteric disease. It is not unusual to see several cases on each of our medical wards. Recently, the Mayo Clinic reported on a series of 1475 cases seen in ten years! It is also to be expected because of the high incidence of dysentery in the present World War zones, that a large number of chronic ulcerative colitis cases will be seen in our armed forces.

Etiology. The term "non-specific ulcerative colitis" is an unfortunate one. We favor "indeterminate ulcerative colitis," defined as an ulcerative inflammation of undetermined etiology. However, careful stool studies over many years by Miss Hirshberger and myself under the supervision of Dr. Gregory Schwartzman have established the fact that this disease is not one entirely without a known cause or even one with a unitary etiology. We have found that a small percentage (about 5 per cent) are unrecognized instances of chronic amebic dysentery. In the past twenty years, three cases of undiagnosed and untreated amebic colitis came to autopsy in this hospital. Because of that and the common difficulty in finding the endameba histolytica in the stools, today we insist on a course of antiamebic therapy (emetine and carbarsone) in every case of so-called "indeterminate ulcerative colitis." Using this therapeutic test, I have collected twenty cases with brilliant and rapid cures. That, I feel, proves the amebic etiology in this group.

Another somewhat larger percentage are probably instances of chronic bacillary dysentery. In one series of sixty-seven consecutive cases, we found dysentery organisms in seven cases. If we add to these the cases with a high dysentery agglutinin titre in the blood and those with an anti-dysentery bacteriophage in the stool (Miss Hirshberger and I found this in one-third of our cases and none in normals), the incidence of chronic bacillary dysentery approaches 15 to 20 per cent in the entire group.

The question next arises—what is the cause in the remaining 75 per cent? We are opposed to the idea that it is Bagen's diplo-streptococcus. We believe he

¹ Read as part of the series "Advances in Medicine" at the Blumenthal Auditorium, The Mount Sinai Hospital, February 2, 1944.

dealt with a mixed group of enterococci. His bacteriology remains largely unconfirmed and the therapy with his vaccine, filtrate, and serum is very disappointing.

Is this disease a psychosomatic disease as several observers in and out of the hospital contend? It must be admitted that psychic factors are often prominent and that occasionally psychotherapy is brilliant. However, the pathological features are identical with chronic amebic and bacillary dysentery. Also, we have not seen the transition from the functional nervous diarrheas and from the so-called mucous colitis (admittedly a psychosomatic disease in most cases) into ulcerative colitis. This phase, I feel, requires further study before drawing the final conclusion that ulcerative colitis is primarily a neurosis.

Dr. Shwartzman and I, after years of clinical and laboratory study, feel that this disease often commences as a specific infection, perhaps a specific dysentery, perhaps *Salmonella*, perhaps *staphylococcus*, and that the inciting organisms soon disappear but sensitize the bowel to subsequent local or distant infections or other harmful influences.

There is the further possibility that ulcerative colitis may be due to a filterable virus. Using the filtered pus from side-tracked colitis colons and injecting it into the peritoneal cavity of young puppies I obtained transmissible, hemorrhagic, intestinal lesions. This work, carried out a few years ago, remains unpublished since further experiments seem desirable.

Recently Moses Paulson of Johns Hopkins suggested a possible relation of some cases of ulcerative colitis to the virus of lymphopathia venereum. We carried out Frei tests in consecutive cases of females with indeterminate ulcerative colitis for a period of two years with uniformly negative results. Yet it is certainly probable that an occasional rare case of primary lymphopathia venereum of the rectum and sigmoid may mimic ulcerative colitis. In concluding this phase, it should be stated that one of the greatest advances yet to be made in this disease is the discovery of its true etiology.

Pathology. We have learned in recent years some points of interest concerning the pathology. Most of the cases commence in the recto-sigmoid region and spread. When severe and diffuse, 20 per cent show involvement of the terminal ileum. There is a current and common misconception that this represents regional ileitis. However, it differs in many important respects. In ulcerative colitis the ileum is thin-walled and dilated. Fistulae are not seen and side-tracking does not cure. In regional ileitis the ileum is thickened, stenosed, fistulae occur in 50 per cent and side-tracking usually heals the lesion.

A fair percentage of colitis cases, perhaps 10 to 15 per cent, commences in the ileo-cecal region. This so-called "right-sided" or proximal ulcerative colitis, often granulomatous, may take many months or even years to reach the rectum.

The localized granulomas (so-called "segmental" type) may eventuate from a diffuse ulcerative colitis or go into it.

Polyposis is a common complication and merits special consideration. Is it an irritation phenomenon? Is it due to a virus? The most important question concerning it however is—do these inflammatory polypi become malignant?

congenital polyposis or adenomatosis is admittedly a pre-cancerous disease probably in 100 per cent of the cases, but how often is this? The Mayo Clinic claims it is not an uncommon sequence. We feel that it is a very rare occurrence. I personally, have seen carcinoma associated with ulcerative colitis only four times. Three cases were without polyposis and, in one healed case, eight years later, multiple polypi with multiple foci of carcinoma occurred. Even this may have been a coincidence.

Liver abscess does not complicate this disease. If present, the case is surely one of amebic origin.

Interestingly enough, amyloidosis practically does not occur. I saw it only once in a severe case, complicated by a huge, chronic, trough-like perineal abscess.

In my opinion, ulcerative colitis is not related to regional ileitis. The few combination cases which have been seen probably represent a mild secondary infection of the colon. I have, however, seen a few cases of ulcerative colitis go on to a diffuse jejuno-ileitis.

Clinical Features. A few clinical features are worthy of mention. A severe case may recover but recurrence, as in peptic ulcer, is the rule. The mortality in this disease, despite all known therapeutic measures, is high (10 to 15 per cent). Fatal perforation occurs in 3 per cent. Toxicity and pathology are not always parallel. Sigmoidoscopy and x-ray examinations are vital not only for diagnosis and localization but also for prognosis.

Therapy. We will now consider briefly the therapeutic phase. Here perhaps some advances can be brought out in the discussion.

Anti-amebic therapy in every case is imperative. If the case is a proved bacillary dysentery, sulfaguanidine and sulfasuxidine are today our best weapons. Antidysentery serum is probably of little value.

The diarrhea is not a true one but consists rather in rectal inflammatory discharges. Hence, restricted diets are unnecessary. Here opium is "the sovereign prince of remedies," as Sydenham put it. Vegetable gums are of some value particularly carob and karaya gums. Medicated enemas are of little value. Of these, the best intestinal antiseptic today is azochloramid. Dr. Rose Spiegel helped some mild chronic cases with cod liver oil rectal instillations. The two, azochloramid and cod liver oil, may be combined.

Repeated transfusions are of the greatest value and form perhaps the single best therapeutic agent in this disease.

About eight years ago, Dr. Schwartzman, using the principles of his phenomenon, developed an anti-toxic *B. coli* crude horse serum for the treatment of surgical peritonitis. It was my idea, since we found in all our cases of ulcerative colitis the harmless enterococcus and the toxic colon bacillus to try this anti-*B. coli* serum in our colitis cases. After some early successes, Dr. Schwartzman prepared a strongly anti-toxic concentrated serum by injecting horses with pooled vaccines and toxins from ulcerative colitis patients. Eighty cases have been treated. Of these cases, all of whom had been refracting to other forms of therapy, 70 per cent gave strikingly good immediate results. The effect on the ultimate course of the disease is now being studied. As a result of our favorable experience, when the

serum is again made available, which E. Lilly & Co. promise us after the war, we advocate its trial on a large scale by the medical profession to determine its real value in a large series of cases.

Since ulcerative colitis seems to be, either primarily or secondarily, a severe infection of the bowel wall and the predominating organism seems to be the coliform bacillus, why shouldn't sulfonamide therapy be of the greatest value? I have tried the several sulfonamides, singly and in combination, and despite a few favorable reports in the literature, I am prepared to state that in my personal experience with a large number of ward and private cases the sulfonamides including sulfasuxidine, to date are not of any special value in the treatment of this disease. There may be a local inhibitory substance (para-amino-benzoic acid?) in the bowel exudate. This explanation for the failure of sulfonamide therapy requires further study.

Three other therapeutic measures which have been proposed in recent years may be mentioned, viz: 1) cabinet hyperpyrexia; 2) intravenous typhoid vaccine and 3) intramuscular liver extract. We have not seen any striking results from any of these.

We believe that we exhaust present day medical therapy when we give the patients a liberal non-residue diet; extra vitamins; opium; transfusions; anti-toxic B. coli serum; and in a few selected cases (especially severe right-sided ones) a so-called "physiologic ileostomy", that is, intravenous fluids, vitamins and transfusions for several days with only water, tea, and broth by mouth.

Surgical Therapy. What progress has been made in surgical therapy? In general, ulcerative colitis is a medical disease. However, surgical therapy is definitely indicated in acute fulminating or life-threatening cases; in chronic, intractable diffuse cases with complications; in "right-sided" ulcerative colitis; and for localized, granulomatous lesions.

We have learned that while a timely ileostomy may save a life in a fulminating case, it does not cure the disease and, once established, it may not be removed else the disease flares up. It is, of course, essential as a preliminary operation to subtotal colectomy.

Subtotal colectomy in stages offers a cure in a small percentage of cases. Only time and a fair trial will tell whether it cures a sufficient number of patients to warrant the fairly high mortality inherent in such multiple, massive procedures.

For the right-sided cases, ileo-sigmoidostomy with proximal colostomy and subsequent resection of the involved area is a logical and fairly successful procedure. Innovated by Dr. A. A. Berg and continued successively by Drs. Colp and Garlock, this procedure is also getting a fair trial. Certain it is, with the exception of an occasional rare case, that the best medical treatment usually fails to cure right-sided ulcerative colitis and surgery becomes necessary.

SUMMARY

We may now summarize our entire discussion briefly by stating that this disease is today very common; crippling; is baffling in its nature; has a high

mortality; that medical therapy has advanced chiefly in transfusion and anti-toxic B. coli serum; and that surgical therapy is still on trial. All in all, ulcerative colitis remains definitely "colitis gravis." To temper this pessimism somewhat, I would like to state that some years ago Dr. E. Arnheim and I found that the medical mortality of the toxic, hospitalized group in a ten year period (1925-1935) was 18 per cent. A few years ago, I reviewed our mortality for a recent five year period and found that it had dropped to 8 per cent. Either the disease is milder or our more advanced therapeutic efforts have been crowned with greater success.

PULMONARY EMBOLUS OF NON-CARDIAC AND NON-POSTOPERATIVE ORIGIN

EDWARD MEILMAN, M.D. AND SELVAN DAVISON, M.D.

[From the Medical Service of Dr. Eli Moschcowitz]

Pulmonary embolism has been drawn from the realm of dramatic unavoidable catastrophies and shown to be not uncommon and even preventable by the efforts of many surgical investigators during the past ten years. The extremely small number of successful cases of pulmonary embolectomy shifted emphasis to prophylaxis and this in turn led to awakened interest in thrombophlebitis and its early recognition and therapy. Since Homans' paper in 1934 (1) the clinical recognition of the milder forms of pulmonary infarction and embolism and its most common source, the deep veins of the leg, has been emphasized. The differentiation of phlebothrombosis from thrombophlebitis (2) has done much to clarify the underlying pathogenesis. It is not yet widely recognized that pulmonary embolism is as much a medical disease as a surgical one. Despite several reports (3, 4, 5) emphasizing this fact, and the diagnosis of pulmonary emboli following thrombophlebitis in non-surgical patients it is not recognized as readily as it should be. Too many physicians still think of pulmonary embolism as a syndrome consisting of chest pain and hemoptysis or sudden death occurring ten days after an operation.

Although most cases of pulmonary embolus occur postoperatively or in patients with heart disease or debilitating illness, it is important to recognize that it can also occur in apparently healthy persons following trivial injury which is often overlooked at the first examination.

This report deals mainly with pulmonary embolus as a non-surgical, non-cardiac problem. The following case study illustrates certain clinical features of this condition.

CASE REPORT

History: (Adm. 492127): A 32 year old man entered the hospital on July 6, 1942 because of shortness of breath and fainting spells for six days. One month before admission he began to experience pain in the left calf which gradually spread toward the knee, thigh and hip during the following week. A diagnosis of "sciatica" was made and he was treated by injections of procaine into the calf without relief. He therefore entered a hospital where x-ray examinations were performed, but no definite disease was found and heat treatments were recommended.

Six days before entering The Mount Sinai Hospital, while in a pool receiving some treatment to his leg, he suddenly fainted. The only premonitory symptom was a brief choking sensation in the substernal region. He had to be assisted home and while there he vomited twice and became quite dyspnoeic. Because of persistent breathlessness and palpitation an electrocardiogram was taken which showed a deep S₁, inverted T₃, inverted P₄ and elevated ST₄. The patient recovered sufficiently so that on the morning of admission he was preparing to go to work when he had an oppressive feeling under the lower sternum and again fainted. His white blood count was 16,000 and the sedimentation time was rapid. The patient was given $\frac{3}{4}$ grain of morphine and sent to the hospital.

Examination: The patient was a well developed and nourished, dyspnoeic, orthopneic, prehensive, with cyanosis of the ears and nail-beds and cool, clammy skin. The temperature was 102.4°F., pulse 130, and respirations 30 per minute. The conjunctivae and sclerae were normal. The pupils reacted normally, ocular movements were normal. Ear, nose and throat examinations were negative. The trachea was in the midline and freely movable. There was no distension of the cervical veins. No adenopathy. The lungs were sonant; the breath sounds were normal; there were no rales; the diaphragm moved normally. The heart was not enlarged except perhaps to the right. There was a soft apical stolic murmur and a gallop rhythm. A_2 was equal to P_2 . The blood pressure was 110 stolic and 80 diastolic. The pulse was regular but weak and thready. Abdominal examination revealed no abnormality. Neurological examination was negative.

Laboratory Data: X-ray examination of the chest shortly after admission revealed no abnormalities. An electrocardiogram showed sinus tachycardia, rate 145; right axis deviation; high P waves (over 2 mm.); small Q_3 and inverted T_3 . The urine contained 1 plus bumin and an occasional granular cast. Blood: hemoglobin, 119 per cent; red blood cells, 20 million; white blood cells, 20,250 with 71 per cent polymorphonuclear leucocytes. Blood urea nitrogen, sugar and icteric index were normal.

Course: The diagnoses suggested were acute myocardial infarction, acute hemorrhagic pancreatitis, pulmonary embolism and rheumatic fever with pericarditis. Most observers favored the last diagnosis and believed that there was no connection between the episode of "sciatica" and the present illness.

The evening of admission, the patient's temperature rose to 103.2°F. and there was a slight improvement in his sense of well-being. His venous pressure was 8 cm. rising to 10 cm. on right upper quadrant pressure. The circulation time (calcium gluconate) was about 2 seconds but the end-point was not well defined. Sedimentation time was rapid, 35 minutes.

The next morning his temperature was 100°F., the gallop rhythm was not audible but peripheral cyanosis and tachycardia persisted and a presystolic murmur at the apex was heard by several examiners. The blood pressure was 95 systolic and 70 diastolic. P_2 was definitely louder than A_2 . A circulation time with calcium gluconate again gave an unsatisfactory end-point but appeared to be over 35 seconds.

At this time the history of leg pain was reinvestigated and it was learned that the pain in the calf followed a fall over a barrel, without direct trauma to the calf. Shortly thereafter, the patient noticed that dorsiflexion of the foot caused pain in the calf (Homans' sign) with radiation into the groin. It was then emphasized that about three weeks after this episode the patient had the first of repeated episodes of pressure in the substernal region followed by faintness, cyanosis, dyspnea and moderate circulatory collapse. An electrocardiogram showed evidence of right heart strain. For these reasons the diagnosis of pulmonary embolism from a focus in the deep veins of the leg seemed more likely. Confirmatory findings not noted on admission were detected on careful examination of the legs. There was definite, although slight, pain and tenderness in the calf and upper leg along the course of the deep veins. The superficial veins on the dorsum of the left foot were slightly distended; those on the right were collapsed. The left calf diameter was $13\frac{1}{4}$ inches, the right was $12\frac{1}{2}$ inches. There was no edema of the left leg, nor was its color different from the right. The toes on both feet were equally cyanotic. This was not considered convincing evidence for thrombophlebitis by most observers.

On the third hospital day the only change detected in the physical examination was that A_2 had become louder than P_2 . Venous pressure was 4 cm. rising to 6 cm. on right upper quadrant pressure and the circulation time (saccharin) had fallen to 17 seconds. That day the patient had a sudden attack of epigastric and substernal pain aggravated by deep breathing and associated with extreme dyspnea, cyanosis and orthopnea. There was coughing productive of a small amount of sputum with one fleck of blood. There was no change in the heart sounds. In a few minutes the pain receded and the patient felt much better. One hour later he had a severe chill with marked cyanosis and dyspnea. His

temperature rose from 100.6°F. to 102.2°F. A blood culture (later reported negative) was taken. The electrocardiogram was repeated and showed a rate of 105, lower QRS voltage, Q₂ no longer present, T₂ iso-electric and ST₄ slightly elevated.

A surgical consultant was called and he agreed that the clinical picture was that of pulmonary embolization secondary to a thrombophlebitis of the deep veins of the left leg and advised exploration of the femoral vein.

The patient was operated on under local anesthesia. The femoral vein was pale white instead of the normal purple and there was inflammatory reaction around it. The lumen was completely occluded by thrombus and it was necessary to extend the exploration upward by division of Poupart's ligament. The external iliac vein was ligated at a site which was normal in appearance and thought to be above the level of the thrombus. A few minutes later the patient suddenly became dyspneic and cyanotic, his pulse became imperceptible and he died despite artificial respiration and stimulation by coramine and intracardiac epinephrine.

Necropsy Findings: A large free-floating embolus was found in the right ventricle. The pulmonary arteries contained many emboli in various stages of organization, including old fibrous endarterial scars representing completely organized thrombi. There was hypertrophy and dilatation of the right auricle and ventricle. The lungs showed hemorrhagic infarcts of both lower lobes. There was thrombophlebitis of the deep venous system of the left leg from the external iliac to the popliteal.

DISCUSSION

We are interested in emphasizing certain clinical features of pulmonary embolism that would make possible earlier recognition of the entity and consequently earlier therapy. Most important is a history of a pulmonary or cardiac episode following leg pain or trauma. Most pulmonary emboli come from a focus arising in the deep veins of the leg (6). Therefore in all suspected instances one must elicit a careful history of possible trauma to any part of the lower extremity. This trauma need not necessarily be recent or severe. It may be so mild as to be described as a "sprain." One must ask whether the patient had any pain in the calf, ankle, sole, or heel of the foot, as well as over the course of the veins in the upper leg. The patient may have noticed some swelling or pain on walking which disappeared on rest.

The presenting symptom may be sudden dyspnea, with or without chest pain, recurrent chest pain suggesting myocardial infarction, syncope, upper abdominal pain, shock or tachycardia. In our case, the patient stated that he had been given injections for sciatica so that this was first thought to have no connection with his chief complaint and he was considered by competent observers to have acute rheumatic fever. With the diagnosis of pulmonary embolism in mind the much more significant history detailed above was obtained. In fact, it should be noted that precisely those patients with milder symptoms are in greater danger of embolization, because a marked inflammatory reaction with more obvious symptoms probably indicates that the thrombus is more firmly organized and therefore better anchored.

Pulmonary infarction is usually characterized by chest pain and hemoptysis, but the hemoptysis may be slight and secondary infection may overshadow it. However, when embolism without infarction has occurred, hemoptysis is absent and the syndrome is less obvious. If questioning has elicited any of the informa-

on mentioned above, confirmation can usually be found in the physical examination.

Although there is no outstanding finding pathognomonic of pulmonary embolism, there are several features which, if considered together, make up the clinical picture. When present, cyanosis, dyspnea, orthopnea and tachycardia may be all out of proportion to the paucity of the pulmonary signs. Our patient had marked cyanosis of the fingertips and toes, tachycardia and some dyspnea, but was otherwise comfortable between attacks. During the attack he became orthopneic, dyspnoeic and intensely cyanotic and complained of pain in the region of the xiphoid. Neither between episodes nor during embolization could any abnormalities be detected in physical examination of the lungs despite the presence of many emboli which filled a large part of the pulmonary artery bed.

When embolism without infarction occurs x-ray examination of the lungs may be completely negative as in this case.

The heart may show only a tachycardia and an accentuated P2. Our case had variable murmurs and at one time a gallop rhythm. He showed a finding that we have since seen in another case. That is a change in the relative intensities of A2 and P2. This may prove to be a useful sign. The sudden change in circulatory dynamics in the pulmonary artery tree due to an embolus causes an increase in pressure which is reflected in a loud P2. In the case described when P2 was greater than or equal to A2 circulation time was quite prolonged; later when A2 was louder than P2 the circulation time was 17 seconds.

The role of the electrocardiogram has been discussed by others (7). The changes may be of much aid in the diagnosis. In this case, the record was considered suggestive of pulmonary embolism. The characteristic changes are prominent S₁, low origin T₁ with staircase ascent in leads I and II, small Q₃ plus inverted T₃.

Upper abdominal pain may confuse the picture, but is significant when considered in relation to the history and especially to certain findings in the legs.

Although all of the following signs may be absent, or if present, apparent only in minor degree, these are diagnostic of thrombophlebitis of the deep veins of the leg (8): a) tenderness in the calf and popliteal space on dorsiflexion of the foot (Homans' sign); b) tenderness along the course of the deep veins; c) increased local heat; d) fullness of superficial veins; e) edema or swelling, which may exhibit itself only as a small but measurably increase in calf diameter; f) slight cyanosis. In our case all of these signs were not present and those found were minimal despite obstruction of the deep venous system from the popliteal to the external iliac vein.

If, when suspicion of pulmonary embolism is entertained, no definite signs of thrombophlebitis can be found, then recourse should be had to venography (9, 10). The technique is not difficult and apparently as harmless as the injection of diodrast for intravenous pyelography.

A discussion of therapy is outside the scope of this paper. Both surgery and

anticoagulant therapy have adherents. Perhaps ligation and evacuation of the thrombus, followed by anticoagulant therapy is most rational.

SUMMARY

A case report illustrating pulmonary embolus as a non-surgical, non-cardiac problem is presented and the clinical features characterizing this condition are emphasized.

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INTRACRANIAL MENINGIOMAS¹

AVRAAM T. KAZAN, M.D.²

and

DANIEL WELLER, M.D.³

[*New York*],

JORGE GOMEZ JARAMILLO, M.D.⁴

[*Medellin, Colombia, S. A.*]

PART II

MENINGIOMAS OF THE SPHENOIDAL RIDGE

These characteristically slow-growing tumors may originate at any point along the sphenoidal ridge. They have been conveniently grouped into three classes: those arising from the inner, middle and outer thirds of the ridge. The proximity of the inner third tumors to the interpeduncular space and its vital structures (fig. 16-3) explains why, when even small, they elicit striking symptoms. On the other hand, even quite large tumors at the outer thirds may be asymptomatic.

In most cases, tumors of the inner third soon manifest themselves by motor and sensory signs and symptoms referable to the damage of cranial nerves in this region; the second, third, fourth, first division of the fifth, and the sixth nerves lie in close proximity to one another here. However, as the mass grows other symptoms caused by pressure and distortion of more distant structures such as the brain stem, tuber cinereum and third ventricle may complicate the picture. Therefore, while unilateral failure of vision, unilateral *nasal* hemianopsia, oculomotor palsies, and exophthalmos on the ipsilateral side are the usual signs, the presence of contralateral pyramidal tract signs and even polyuria and adiposity should not be allowed to mask the picture. Headaches, personality changes and paresthesias in the distribution of the first division of the fifth nerve are also found. Irritation of the uncinate gyrus may give rise to fits characterized by olfactory or gustatory hallucinations associated with the "déjà vu" phenomenon. X-ray examination frequently shows erosion, absorption or eburnation of the sphenoidal ridge with corresponding changes in the outlines of the sphenoidal sinuses.

Tumors of the middle third of the sphenoidal ridge (fig. 16-4) may spread beyond their point of origin and invade the temporal as well as the frontal lobes. When the walls of the orbit and the retroorbital tissues are invaded, there is unilateral proptosis, frequently in conjunction with ipsilateral optic atrophy. This is a very characteristic meningioma syndrome. Unilateral (or bilateral) im-

¹ From the Neuropathology Laboratory, The Neurological and Neurosurgical Services of The Mount Sinai Hospital, New York.

² Former Resident in Neurology, The Mount Sinai Hospital, New York, now Lt. A. T. Kazan, MC, A.U.S.

³ Voluntary Assistant in Neuropathology, Mount Sinai Hospital, New York.

⁴ Fellow, Dazian Foundation for Medical Research.

pairment of olfactory sense associated with slowly progressing contralateral homonymous hemianopsia is another clinical pattern. Rarely, hallucination in the visual and olfactory spheres, aphasia and mental changes, contralateral facial palsy, and hemiparesis with hyperreflexia have been noted.

Tumors of the outer third (fig. 16-5) arising from the pterional ridge fall into two classes: the "en plaque", characterized by their flat growth and exaggerated hyperostosing qualities, and the "global", non-hyperostosing and usually projecting into the Sylvian fissure. Meningiomas "en plaque" involve mainly the ala magna of the sphenoid and lie in close relation to the middle meningeal artery, the sinus parieto-sphenoidalis and some of the Sylvian veins. Early symptoms of this group are: occipito-frontal headaches and intraorbital discomfort with impairment of vision in the ipsilateral eye; diplopia, lacrimation and photophobia are not infrequent. Physical signs such as forward and downward displacement of the eyeball, edema of the eyelids and fullness of the suprazygomatic region may be present. Ophthalmoscopic examination of the fundus often discloses papilledema, increased vascularity and even secondary atrophy of the nerve-head. Roentgenologic evidence of bony thickening of the wings of the sphenoid and involvement of the floor of the middle fossa confirms the diagnosis.

Global meningiomas are likewise found at the pterional end of the ridge and, because of their relation to the Sylvian fissure, are called "Sylvian point" tumors. They also lie in close relation to the important vessels of that region such as the middle cerebral and meningeal arteries and the Sylvian veins. As noted, these neoplasms grow spherically and affect the bone but little. While small, they may remain undetected for long periods, but ultimately they attain enormous size (5-7 cm. in diameter) and distort the brain by pushing the temporal and frontal lobes apart. Their presence may then be attested by headaches, convulsions, dimness of vision and somnolence. Even in the later stages, they show no uniformity of symptoms and give rise to no characteristic syndrome. In some instances, Jacksonian seizures unassociated with loss of consciousness and involving the contralateral side of the face and mouth occur. Irritative effects of the tumor on the temporal lobe may provoke visual hallucinations of complex formed images. Homonymous field defects, exophthalmos and a contralateral facial weakness may be found. Bilateral choked discs are quite common. The symptomatology of the tumor may vary on the two sides, since those on the left more often show paraphasia and anomia. Roentgenologic studies may disclose changes in the pterion varying from an intense vascularity to a slight regional honey-combing of the bone. Occasionally, there may be absorption of the sella.

Case 6. Meningioma of the sphenoidal ridge—global.

History (Adm. 363949; P.M. 9130). A woman, aged 56 years, entered The Mount Sinai Hospital on April 2, 1934. Two years before her admission she had a convulsion involving her entire body and lasting a few minutes. Six months later there was a similar seizure which lasted several hours and since that time she experienced brief seizures about once a month. Personality change characterized by a hypomanic reaction set in a year before admission. Recently difficulty in word-finding had been noted and two days before admission drowsiness, slurring of speech and stiff neck developed.

Examination. The blood pressure was 170 systolic and 110 diastolic. The patient was semi-stuporous. The left fundus showed slight swelling of the disc, sclerotic vessels and a flame-shaped hemorrhage; there was paralysis of the right external rectus; the right nasobuccal fold was less clearly defined than the left. Nuchal rigidity was present. Deep reflexes were active; abdominal reflexes were not elicited. Left Babinski and Oppenheim signs were found.

Course. The diagnosis of a right fronto-parietal brain tumor was made. Lumbar puncture revealed clear cerebrospinal fluid under an initial pressure of 260 mm. of water. Total protein was 77 mg. per cent. On ventriculography the ventricles failed to fill. A week following admission the patient died of pneumonia.

Necropsy findings. Brain. Gross: The calvarium was thickened in the left temporo-parietal area. A large firm tumor, about 8 cm. in diameter, sharply demarcated from the adjacent brain tissue occupied the left fronto-temporal area and lay in part in the middle

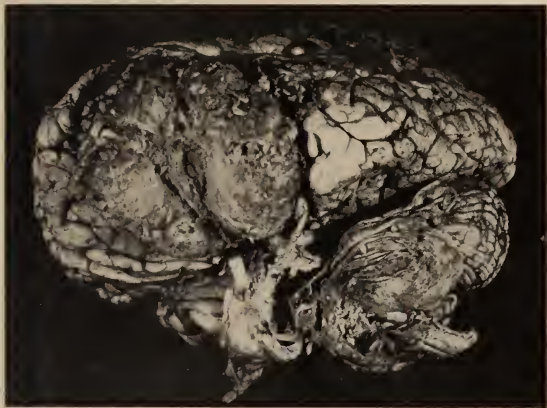


FIG. 19. Sphenoidal ridge meningioma—leptomeningioma (see Fig. 7)

fossa (fig. 19). The dura could not be separated from the tumor; all the bony prominences of the left middle fossa were found to be smoothed and leveled out.

Microscopic: Sections of the tumor showed the cells to be arranged in concentric circles or in whorl-like formations. In other parts of the tumor, the cells were surrounded by connective tissue. Some capillaries were empty, others were occupied by many red blood cells. A small cluster of foam-cells was seen surrounded by arachnoidal cells, and a few xanthoma bodies were found near a zone of disintegrated tissue (fig. 7). The capsule of the tumor was formed by a structure resembling the dura.

Diagnosis. Leptomeningioma.

Comment. The significance of epileptiform seizures and personality changes beginning in adult life is illustrated here. As in many of these cases, neurological examination did not serve to localize the tumor positively, but the central facial weakness on the right and the definite history of anomia in a right-handed individual tended to place it in the left hemisphere. The left Babinski sign and the right abducens palsy were confusing. Had the thickening of the calvaria

on the left side overlying the tumor been noted on the x-ray examination, an incorrect localizing diagnosis might have been avoided.

INFRATEMPORAL MENINGIOMAS

These tumors are few in number, histologically variable, and arise from the dura of the horizontal floor of the middle fossa (fig. 16-6). Situated in a "silent region", they may attain large dimensions before localizing symptoms appear. Large growths often distort the chiasm, pons and cerebellar peduncles initiating symptoms suggestive of cerebellar lesions such as positive Romberg sign, nystagmus, and hypotonia. Clinically, these tumors present no characteristic syndrome—indeed evidence of brain tumor without any hint of localization might well arouse suspicion of an infratemporal tumor. At times their presence is marked by unilateral headache, vomiting, vertigo and dimness of vision. Marked aphasia and impaired mentality point to a left sided lesion. In rare cases convulsive seizures, diplopia, diminished olfactory sense, contralateral facial weakness, and contralateral homonymous quadrantic field defects have been recorded. Also infrequently uncinat fits with hallucinations of taste and smell, "déjà vu" phenomena, and motor manifestations such as swallowing and licking movements of the lips may be produced.

MENINGIOMAS OF THE CAVUM MECKELII

Meningiomas of the cavum Meckelii have been variously called Gasserian endotheliomas, fibrosarcomas and fibroendotheliomas. They are usually found straddling the anterior end of the petrous ridge (fig. 16-7), presenting themselves both on the supra- and infratentorial surfaces. In most cases, they are intimately attached to the coverings of the Gasserian ganglion. The gassero-petrosal syndrome is produced by reason of the proximity of the third, fifth and eighth nerves to the lesion. This syndrome is characterized by ipsilateral paresthesias and anesthesia dolorosa in the trigeminal field, corneal ulcerations, ipsilateral oculomotor palsies, ptosis and slight exophthalmos (cf. Case 10). In the later stages, tinnitus, impaired hearing and a sense of fullness in the ear may develop. If the lesion extends over the petrous ridge into the posterior fossa headache, choked disc and facial palsy may result. Should the pons be compressed and deformed, motor instability, nystagmus and ataxia usually follow.

Case 7. Meningioma of the cavum meckelii.

History (Adm. 457778; S-71139). A man, aged 21 years, was admitted to The Mount Sinai Hospital on June 20, 1940. Two years before entering the hospital he noted the onset of numbness in the right upper lip. This numbness was sudden in onset and soon spread over the entire right side of the face. About a year before admission he developed paresthesias of the right side of his face and epiphora of the right eye. During that year also he noted slight weakness in right sided mastication, slurring of speech, and clumsiness of the tongue. Six weeks before entry there was onset of blurring of vision and diplopia.

Examination. There was slight ptosis of the right upper lid; the right pupil was larger than the left and there was paresis of the muscles innervated by the right oculomotor nerve. Diplopia was present on looking in all directions except to the left and down. Marked motor and sensory involvement of the right trigeminal nerve was present. There was left-sided pyramidal tract signs.

Course. Lumbar puncture showed normal pressures and dynamics; cerebrospinal fluid total protein was 58 mg. per cent. Caloric tests disclosed slight diminution of vestibular responses on the right side. Electroencephalography was normal. An exploratory craniotomy was performed and revealed a tumor involving the right Gasserian ganglion.

Pathological report. The tumor was highly cellular and was composed of elongated cells ranged in groups and whorls. The dura had been invaded by the tumor. Some remnants degenerated sensory cells of the Gasserian ganglion were still to be seen. The tumor was intravascular.

Diagnosis. Leptomeningioma.

Comment. The long duration of symptoms is to be noted. The characteristic sequence of events in tumors of the Gasserian ganglion sheaths is illustrated here with the successive involvement of the sensory, then the motor branches of the fifth nerve. The later development of almost complete right ophthalmoplegia and signs of left pyramidal tract involvement point to the extension of the growth into the region of the right cerebral peduncle at which point only a single lesion may encroach upon both the right suprabulbar motor tracts and the right third nerve.

PERITORCULAR MENINGIOMAS

Peritorcular meningiomas are situated near the torcula Herophilii or confluence of the sagittal, lateral, straight and occipital sinuses (fig. 16-8); they originate in many instances from the posterior end of the superior sagittal sinus. Because of the danger of hemorrhage, the hazard incident to the removal of tumors in this location is greatly increased. Most of them show a characteristic angio-elastic pattern with a tendency to rapid growth and early recurrence after surgical removal. By virtue of their situation opposite the calcarine fissure and the cuneate lobe, such growths produce visual field defects which are, indeed, their most striking and consistent symptom. Perimetric studies have shown that the lower quadrants of the retinae have their representation in the upper lips of the calcarine fissure and, conversely, the upper quadrants in the lower lips; the macular region is projected on the posterior aspect of the fissure at the occipital pole. It is to be remembered that a late effect of tumors implicating the occipital lobe may be a bilateral hemianopic defect due to pressure on the occipital end stations of vision. Occasionally, central scotomata have been found. If the cerebellum is involved by the growth, the tumors may cause suboccipital discomfort, vomiting, tenderness or stiffness of the neck, posturing of the head, and unsteadiness of gait.

Case 8. Peritorcular meningioma.

History (Adm. 301390; P.M. 6710). H. E., a 42 year old white man, was admitted to The Mount Sinai Hospital in May 1929. He was well until 3 months before admission when he began to have paroxysmal occipital headaches. Two months later he developed blurring of vision of his right eye. Two days before coming to the hospital he experienced episodes during which he felt powerless to move; these lasted only two to three minutes and were not accompanied by loss of consciousness.

Examination. The blood pressure was 152 systolic and 100 diastolic. The gait was lightly ataxic and there was bilateral diminution of associated movements. Examination of the fundi disclosed bilateral papilledema. The visual fields were normal. Nystagmus

was present on right lateral and upward gaze. There was questionable right facial weakness. The deep reflexes on the left were more active than on the right; the left abdominal reflexes were diminished. A questionable Babinski sign was noted on the left.

Course. The cerebrospinal fluid was not remarkable except for an initial pressure of 240 mm. of water; there was markedly diminished rise in cerebrospinal fluid pressure following bilateral jugular vein compression. In the caloric tests, stimulation of the right ear increased the left lateral nystagmus; stimulation of the left ear increased nystagmus in all directions. Pneumoencephalography was attempted but the patient reacted poorly and



FIG. 20. Peritorcular meningioma—pial hemangioendotheliomatous

the procedure had to be discontinued. Two weeks after admission the patient began to complain of increase in the severity of the attacks of weakness and they became associated with profuse diaphoresis and chills. A ventricular puncture was done and fluid under greatly increased pressure was withdrawn; air studies showed both lateral ventricles to be dilated. Dye introduced into the right lateral ventricle was recovered from the left side, but was not found in the cerebrospinal fluid. Four days after the dye injection, the patient's temperature rose to 103° F., rigidity of the neck developed, and lumbar puncture disclosed xanthochromic cerebrospinal fluid containing 1000 leucocytes with 70 per cent polymorphonuclear cells. The patient died seven days later.

Necropsy findings. Brain. Gross: There was a recent subarachnoid hemorrhage overlying the left parieto-occipital region. The left cerebellar hemisphere was enlarged and an encapsulated tumor mass was noted partially buried in it (fig. 20). The tumor appeared to arise from the dura covering the left lateral sinus; it completely occluded this channel. The growth was about the size of a walnut and had a clean bed in the cerebellar substance.

Microscopic: Sections of the tumor showed a densely cellular growth which was well encapsulated and which contained a striking number of blood vessels and sinuses. The cells were elongated, elliptical and were tightly packed into strands. No mitotic figures were seen.

Diagnosis. Meningioma piale, hemangioendothelioma.

Comment. This case did not show the typical picture of peritrolear tumors insofar as the involvement was primarily of the cerebellum rather than of the occipital lobes. The clinical picture, however, did suggest a posterior fossa tumor. The pyramidal tract changes and nystagmus were probably due to brain stem compression. The failure to recover the dye injected into the ventricles from the spinal canal, and the dilatation of both lateral ventricles seen in the autopsies also indicated an obstruction in the distal part of the ventricular system, probably due to compression of the iter. Angioblastic growths such as this one are commonly found in tumors in or near the posterior fossa.

MENINGIOMAS OF THE CEREBELLAR CHAMBER

These tumors generally arise from the meninges at one of several places: 1) from the dura at a point along the basilar or lateral recesses; 2) from the tentorial or subtentorial surfaces of the dura; 3) from the sinuses themselves and, in numerous instances; 4) from the posterior aspect of the hemispheres without definite attachment to either the dura or the sinuses. They are classified by Rushing as the basilar, cerebello-pontine angle and subtentorial types. It seems better to use the term "cerebellar" rather than "subtentorial" to cover posterior fossa neoplasms exclusive of the basilar and angle groups. Most of the tumors which will here be designated "cerebellar" are of pial origin, very vascular, and are found actually within the substance of the cerebellum.

Meningiomas of the basilar groove usually arise from the anterior rim of the foramen magnum, although they may present themselves anywhere along the basilar groove from the foramen magnum to the body of the sphenoid (fig. 16-9). They produce symptoms common to the usual syndrome of cerebellar tumors, but, in addition, often cause pareses and paresthesias of the extremities and trunk. Complete quadriplegias have been described. Symptoms caused by compression of the ninth, tenth, eleventh and twelfth cranial nerves are often combined with sphincteric disturbances and Horner syndromes. Basilar groove tumors are rare and inaccessible to surgical intervention. No tumor in this region occurred in our series.

Cerebellar (subtentorial) meningiomas are those found on the cerebellar convexities or the under surface of the tentorium along the transverse sinus. In rare instances they arise from the sigmoid sinus. Clinically, patients usually complain of severe occipito-frontal headaches, stiff neck, and discomfort with tenderness of the cervical muscles. The gait is titubating toward the side of the tumor

or, should the vermis be involved, the patient may pitch forward or backward. Hypotonia is unilateral (on the side of the lesion) but may be bilateral in midline lesions. The Romberg sign is frequently positive, and generalized convulsions marked by extensor rigidity of the legs, flexion and extension of the arms, an opisthotonus sometimes appear. Dystonia, dysmetria, asthenia and dysidiadochokinesis as well as nystagmus and skew deviation often occur. Papilledema is very common; together with an abducens palsy it may form the only sign of cranial nerve involvement. Pyramidal tract signs and weakness may result from pressure on the pons.

Case 9. Cerebellar meningioma.

History (Adm. 298353; P.M. 6542). A. M., a man aged 49 years, was admitted to The Mount Sinai Hospital on January 3, 1929 complaining of occipito-frontal headaches of one year duration. Six months prior to admission deafness of the left ear developed and in the two weeks before he presented himself he had dizziness associated with nausea and blindness in the left eye.



Fig. 21. Cerebellar meningioma—leptomeningioma

Examination. The blood pressure was 190 systolic and 130 diastolic. He was mentally alert. The pupils reacted normally. There was bilateral papilledema and hemorrhage were present in both fundi. There was complete blindness of the left eye with partial blindness (nasal field) in the right eye. The pupils reacted normally and nystagmoid movements were evident in the left eye on left lateral gaze. A slight left peripheral facial weakness was present. There was a tremor of the extended hands, with ataxia in both upper extremities. The deep reflexes were diminished; the abdominal reflexes were absent; there was a positive Babinski sign on the right.

Course. A lumbar puncture was performed under an initial pressure of 360 mm. of water; the cerebrospinal fluid was clear and contained no cells. Ventriculographic studies showed marked symmetrical internal hydrocephalus and suggested an obstruction in the region of the aqueduct of Sylvius or the fourth ventricle. A diagnosis of left pontofacial angle tumor was made, but the patient refused operation. He developed a bronchopneumonia and died one week after admission of the intercurrent infection.

Necropsy findings. Brain. Gross: The brain was of average size and showed moderate flattening of the convolutions. The left cerebellar hemisphere was swollen and was of increased consistency particularly on the mesial aspect of the posterior lobe. On sectioning a solid tumor, round in outline and measuring about 2.5 cm. in diameter was found in the left cerebellar hemisphere (fig. 21). The lateral and third ventricles and aqueduct of Sylvius were moderately dilated.

Microscopic: Sections showed a densely cellular tumor with extensive areas of hemorrhage.

age and degeneration. The cells, which were of a well differentiated type, were arranged in masses and sheets; no mitotic figures were seen. There were numerous thin-walled blood vessels, and a well-defined stroma was noted (fig. 8).

Diagnosis. Meningioma piale, hemangioendotheliomatous.

Comment. The course of this patient's illness was not typical of posterior fossa tumors. The visual impairment and diminished deep reflexes were mostly due to the chronically increased intracranial pressure. Although this case was diagnosed as a ponto-facial angle tumor, the late development of deafness, the absence of tinnitus and the preservation of the corneal reflexes were against such a diagnosis. The vascular histologic picture characteristic of most posterior fossa meningiomas is again noted here.

Cerebello-pontine angle meningiomas arise between the porus acousticus and the dural opening of the trigeminal nerve (fig. 16-10). Because of their gross resemblance to the acoustic neurinomas and the neurofibromas they have sometimes erroneously been classified as such. Headache and visual disturbances due to increased intracranial pressure are early manifestations. Later there follow localizing symptoms such as ipsilateral deafness, giddy sensations and thermic nystagmus reflecting involvement of both branches of the eighth nerve. As the tumor expands the upper division of the fifth nerve and the seventh nerve become involved. The sixth nerve is rarely affected. Facial weakness is more common than paralysis while ipsilateral cerebellar symptoms and minor degrees of contralateral pyramidal disturbances have often been noted.

Case 10. Cerebello-pontine angle meningioma.

History (Adm. 315202; P.M. 7249). G. G., a woman, aged 52 years, entered The Mount Sinai Hospital on June 12, 1930. She complained of tinnitus in the left ear of two years duration, pain and paresthesias in the left cheek, forehead and jaw of one year's duration and an unsteady gait for the past three months.

Examination. The blood pressure was 160 systolic and 100 diastolic. The patient was ill and irritable. There was a guarded gait with a tendency to fall to the right. The cranial nerves showed spontaneous nystagmus on left lateral gaze, ptosis of the left upper lid, loss of all sensation in the left trigeminal area, paresis of the left external rectus muscle, left peripheral facial paralysis, impaired hearing on the left and deviation of the lower jaw to the left. Muscular power was intact, but there was an irregular coarse tremor in all limbs. There was generalized hyperreflexia most marked on the right; the abdominal reflexes were absent. A Babinski sign was present on the right.

Course. A lumbar puncture performed shortly after admission revealed cerebrospinal fluid under normal pressure. The diagnosis of tumor in the left middle or posterior fossa, probably involving the Gasserian ganglion, was made, but while the patient was under preliminary observation she suddenly developed pulmonary edema and died on the third hospital day.

Necropsy findings. Brain. Gross: A circumscribed tumor about the size of a plum was found in the left ponto-facial angle (fig. 22). It compressed the left side of the pons, the adjoining medulla and the left cerebellar lobe. On its lateral aspect, the tumor was intimately connected with and apparently arose from the adjacent dura. The left fifth nerve was markedly compressed, the left sixth, seventh, eighth and ninth nerves could not definitely be made out.

Microscopic: Sections of the tumor showed a densely cellular structure. The cells were uniform and arranged in masses or strands. There were extensive areas of tumor composed of small cell nests inclosed in thick masses of collagenous fibrous tissue.

Diagnosis. Pachyleptomeningioma.

Comment. The long history of buzzing in the ear suggests an acoustic neuroma, but the pain and paresthesias in the distribution of all three branches of the fifth nerve would be unusual for this syndrome. Clinically, the involvement of the fifth (motor and sensory), sixth, peripheral seventh and eighth nerves on the left side speaks for an acoustic neurinoma or a tumor arising from the Gasserian ganglion—at any rate, a tumor straddling the petrous ridge. The nystagmus indicates brain stem compression. The clinical picture actually best fit

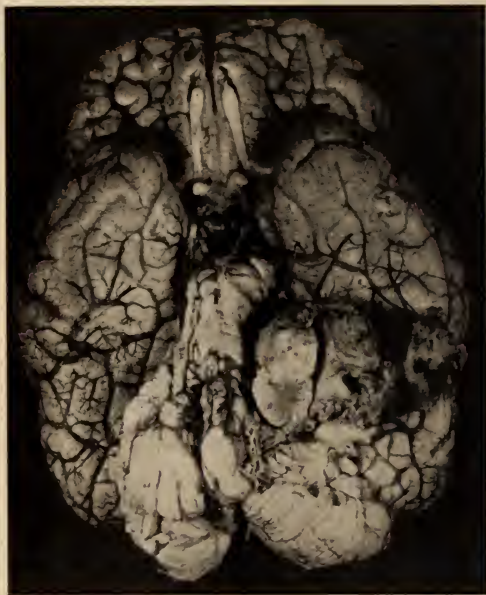


FIG. 22. Ponto-facial angle meningioma—pachyleptomeningioma

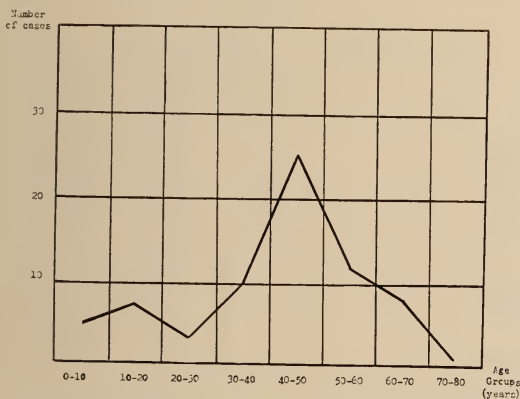
the gassero-petrosal syndrome described above. The post-mortem discovery of an angle meningioma instead of an acoustic neurinoma was surprising.

DISCUSSION

For a clearer understanding of both the anatomical features and the clinical behavior of meningiomas, it is necessary to consider a few additional characteristics of these tumors. These characteristics can best be evaluated by an analysis of a large group of meningiomas, seventy-four of which were verified by post-mortem examination and ninety of which were proven by biopsy. They will be discussed under a variety of headings.

Incidence. The incidence of brain tumor at general autopsies is usually considered as 1 per cent and it is commonly stated that meningiomas comprise some per cent of all forms of brain tumor (6). However, because of the existence of a neurological and a neurosurgical service at The Mount Sinai Hospital and the attraction of just such material, there has been a considerable increase in the percentages both of brain tumors and, specifically, of meningiomas. Thus, out of 9,696 autopsies performed at this hospital over a period of twenty years, brain tumors of one variety or another constituted 4.4 per cent (431 cases). Of these tumors, 17.1 per cent (74 cases) were meningiomas.

Age and sex. The accompanying chart (Graph 1) seems to indicate that meningiomas usually affect people in the middle age groups. Thirty-three per cent of the patients were between 41 and 50 years of age, while 78 per cent of the total



GRAPH 1. Curve showing age incidence in 74 cases of meningioma coming to post-mortem

number were over 30 years of age. Of some significance is the observation that half of the patients under 30 years of age, the tumors were of the sarcomatous variety. Although there was a slight preponderance of females in our series (58 women to 76 men), the six-to-four female-male ratio noted by Cushing (2) was not found.

Anatomic distribution. In 295 cerebral meningiomas collected by Cushing, the anatomical distribution (Table 1) was such as to indicate that the tumors arising from the convexities (including parasagittal) and those arising from the base were approximately equal in number (42 per cent and 47 per cent respectively), while posterior fossa tumors aggregated only 8 per cent. In our smaller series, the distribution was somewhat different: the convexity tumors totaled 51 per cent, base tumors 25 per cent, posterior fossa tumors 18 per cent, and there was a miscellaneous group comprising 6 per cent (Table 1). The finding of a larger percentage of tumors arising from over the convexities would seem to

favor the Globus theory of the primitive meningeal origin of these tumors. Since they arise from the undifferentiated mesenchyme and not from any ripe meningeal product such as the dural sinuses, it is reasonable to assume that meningiomas should be found with approximately equal frequency throughout all meninges. The much higher percentage of posterior fossa neoplasms noted in this series simply indicates that many cerebellar hemangiomas which are not usually considered as meningiomas have, following the classification employed here, been included in this group.

Histologic types. The microscopic investigation of the meningiomas under study revealed that 45 per cent were primarily of pial variety, 28 per cent of the arachnoid variety, while 10 per cent were sarcomatous in character (Table 2).

TABLE 1
Anatomical distribution of meningiomas

SITE	CUSHING		MOUNT SINAI	
	Total cases	Per cent	Total cases	Per cent
Parasagittal.....	65	22.0	16	11.0
Convexity.....	54	18.0	56	37.0
Sphenoidal ridge.....	53	18.0	12	8.0
Olfactory groove.....	29	10.0	10	7.0
Suprasellar.....	28	9.0	7	5.0
Posterior fossa.....	23	8.0	28	18.0
Peritrochlear.....	12	5.0	1	0.7
Temporal fossa.....	8	3.0	2	1.3
Falx.....	7	2.0	4	2.7
Without dural attachment.....	6	2.0	2	1.3
Cavum Meckelii.....	5	1.5	2	1.3
Intraorbital.....	1	0.3	2	1.3
Diffuse.....	0	0.0	3	2.0
With neurinomas.....	2	0.6	0	0.0
Multiple.....	2	0.6	5	3.4
Total cases.....	295	100.0	150	100.0

The remaining 17 per cent was made up of omneforme, mesenchymatous, pachymeningiomatous and mixed varieties. It will be noted that the figure for the incidence of sarcomatous meningiomas is considerably higher than that usually given.

Clinical characteristics. The symptomatology of meningiomas has already been described in the foregoing account. It may be said in summary that meningiomas of the convexities are for the most part clinically indistinguishable from other brain tumors similarly placed; on the other hand, meningiomas at the base lend themselves more readily to diagnosis because of their fairly typical constellations of signs and symptoms. Practically all meningiomas are distinguished from gliogenous or metastatic tumors by reason of their relatively longer histories. Stories going back over five years are not at all rare. For example,

ht of the ten illustrative cases described herein had had symptoms for at least year. The average symptomatic period of the ten cases was twenty months.

Physical findings. There are few physical findings pathognomonic of meningiomas. As a rule, patients with this lesion are better preserved both mentally and physically than those with either primary gliogenous or metastatic brain tumors. The more characteristic features are: 1) large exostoses of the skull, and 2) large plexiform veins in the scalp or temporal regions. The latter are found usually in highly vascular subcalvarial neoplasms.

Cerebrospinal fluid. The initial pressure varies so much that great importance cannot be assigned to it; however, it is usually slightly elevated (about 180 to 200 mm. of water). In our group of cases, it ranged from 80 mm. to over 360 mm. The total protein content of the cerebrospinal fluid is usually slightly

TABLE 2
Incidence of histological types of meningiomas

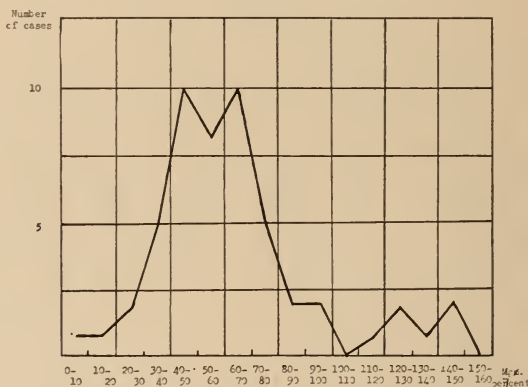
	POST-MORTEM		SURGERY		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
<i>all</i>	33	44.6	43	47.8	76	46.4
a) Hemangioendotheliomatous.....	16	21.6	25	27.8	41	25.0
b) Hemangiomatous.....	11	14.8	13	14.4	24	14.7
c) Psammomatous.....	4	5.4	5	5.6	9	5.5
d) Melanomatous.....	2	2.8	0	0.0	2	1.2
ptomeningiomas.....	17	22.8	29	32.3	46	28.3
arcomatous.....	10	13.5	6	6.7	16	9.7
chymeningiomas.....	5	6.7	3	3.3	8	4.8
eschymatous.....	3	4.1	2	2.2	5	3.0
nniforme.....	1	1.4	3	3.3	4	2.4
chyleptomeningiomas.....	2	2.8	2	2.2	4	2.4
nclassified.....	3	4.1	2	2.2	5	3.0
Total.....	74	100.0	90	100.0	164	100.0

evated. Of 50 cases, 26 had readings between 40 and 70 mg. per cent, i. e., high normal or moderately elevated; of the remaining 24, 9 ranged between 9 and 30 mg. per cent and 15 were between 71 and 146 mg. per cent (Graph 2). The attachment of the tumors on either the subarachnoid or ventricular spaces causing stasis of the cerebrospinal fluid and irritation of ependyma or meninges is apparently the chief cause of the elevation of the protein content. The other chemistries, cell counts, and colloidal gold curves are usually normal.

Roentgenologic findings. Bony changes visualized through x-rays are of peculiar importance in the diagnosis of meningiomas. As has been described above, calcification may occur actually within these tumor; bones from the endosteal primordium may be formed at some point in their substance (e.g., meningioma omneforme); or there may be diffuse calcification as found in psam-

omatous growths. On the other hand, the changes may be predominantly the bone contiguous to the tumor. Pressure causes resorption of bone while infiltration by tumor cells causes irritation and consequent proliferation. Recently it has been argued that since bony thickening often appears before neoplastic infiltration of the bone can be demonstrated histologically, the hyperostosis may be a result of local bony vascular stasis. This contention is borne out by the frequency with which extensive dilatation of diploic and other vascular channels are found on x-ray examination. It has already been remarked that the meningiomas causing most marked bony changes in the skull are the parasagittal and the lateral sphenoidal ridge lesions.

Pneumoencephalograms and ventriculograms are of proven service in the localization of brain tumors. They are, obviously, of little help in determining



GRAPH 2. Curve showing total protein values in 50 random cases of meningioma

the histologic character of the growth. The same may be said about the changes in the position of the pineal body when this structure shows up on roentgenography.

Electroencephalography. Electroencephalograms (EEGs) were obtained in 24 of the cases reviewed; 19 of these showed abnormal records. Of the 5 records which were "normal", 3 occurred in tumors located at the base of the brain (2 sphenoidal ridge, 1 cavum Meckelii) and 2 in tumors of the convexities. Of the 9 meningiomas of the lateral convexities with abnormal EEGs, the test localized the tumor correctly in 8 cases. Out of a group of 5 parasagittal meningiomas a correct EEG focus was found in 4 cases; 3 olfactory groove meningiomas were localized as midline frontal lobe lesions. Two cases of cerebellar meningiomas showed diffuse cerebral dysfunction in the EEG.

half of the abnormal records showed a small degree of abnormality: i.e., relatively high frequency (3 or more per second), low amplitude of delta waves (up to microvolts), and a relatively small amount of delta activity (up to 30 per cent the total length of the record). The other half showed a high degree of abnormality. The cases of the group with high EEG activity tended to be histologically of a more rapidly growing and more vascular type than those with abnormality.⁸

SUMMARY

The results of a study of meningiomas with special emphasis on their histogenesis, morphology, and clinical manifestations are presented. The histologic classification of Globus and the clinical classification of Cushing are reviewed. They, when taken together, are supplementary and offer the clearest, most comprehensive, and most workable basis for the recognition, localization and final diagnosis of intracranial meningiomas.

The authors are especially grateful to Dr. Joseph H. Globus for his constant help and encouragement in the preparation of this paper.

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⁸ The EEG figures are taken from the records of Dr. Hans Strauss, to whom the authors wish to express their thanks.

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NEWS AND NOTES

PORTRAIT OF DR. ISIDORE FRIESNER PRESENTED TO THE MOUNT SINAI HOSPITAL

In commemoration of the seventieth birthday of Dr. Isidore Friesner, former President of the Medical Board of the Mount Sinai Hospital and Consulting Otolologist to the Hospital, a portrait of Dr. Friesner was presented on Thursday, April 27th to the Board of Trustees for the permanent exhibit at the Hospital. The portrait, painted by Alphaeus P. Cole, N.A., was commissioned as a tribute to Dr. Friesner's twenty-four years of service as physician and teacher at Mount Sinai, and in recognition of his pioneer work in establishing the relation of otology to general medicine.

Born in New York City in 1874, Isidore Friesner graduated from the College of the City of New York in 1894 and from the Gross Medical School, in Colorado in 1901. He joined The Mount Sinai Hospital Medical Staff in 1920 and became Consulting Otolologist to the Hospital a year later. He was President of the Hospital's Medical Board from 1927 to 1938. During his direction of the Otolological Department, the training of residents in this field was started at the Hospital. Otolological surgery was greatly improved, knowledge of conditions causing inflammation of the ear was broadened, and the work of his department attracted the attention of the medical profession nationally. He was one of the first to recognize the importance of microscopic studies in ear diseases, and was responsible for the establishment at the Hospital of a Histopathological Department and laboratory facilities in connection with otology in 1928. In 1936 he was appointed Consulting Otolologist to the Hospital. In 1939 he was elected President of the American Otolological Society, and is at present Secretary of the organization.

The portrait was presented for the Board of Trustees by Arthur Harlow, who had arranged for its painting. It was accepted for Mount Sinai by Waldemar Lops, who discussed Dr. Friesner's contributions and stated:—"Perhaps his greatest gift lies in his capacity for developing a critical clinical sense in the men working under him. As a teacher, Dr. Friesner has an infinite ability to stimulate the younger men and a genius for training them in logical thinking. His broad medical interests have been an effective means of arousing interest in the relation of ear diseases to general medicine."

Dr. Friesner thanked the Trustees for their tribute and expressed his pleasure in the portrait and in the work of Mr. Cole. "I realize, of course, that this is not really a personal tribute to me," he said. "It is a tribute to the physicians and surgeons, whose elected representative I was for so many years, who have carried on the work here, and have established, maintained and enhanced the reputation of our institution. I have only one regret—that I no longer have another quarter of a century of active life in which to continue my efforts on behalf of the Hospital, the public, and my colleagues, particularly the younger men whom I enjoyed teaching so much."

Notable among Dr. Friesner's contributions to medicine have been his mi-

croscopic studies of diseases of the ear, which contributed greatly to the treatment of mastoiditis and its complications. He has also made important contributions on the relation of the inner ear to neurological diagnosis. In collaboration with Alfred Brown, he wrote the first book in the English language on the internal e



DR. ISIDORE FRIESNER

"The Labyrinth: An aid to the Study of Inflammations of the Internal Ear" in 1913; and three years later, he wrote one of the leading works on Cerebellar Abscess, again in collaboration with Dr. Brown: "Cerebellar Abscess: Its Etiology, Pathology, Diagnosis and Treatment Including Anatomy, and Physiology of the Cerebellum."

A. A. BERG PRESENTS LABORATORY BUILDING TO MOUNT SINAI HOSPITAL;
GIFT TO BE USED FOR RESEARCH AND MEDICAL EDUCATION CENTER

In April, The Mount Sinai Hospital received a large fund, the gift of Dr. A. A. Berg, Consulting Surgeon to the Hospital and President Elect of the International College of Surgeons. Dr. Berg's gift, presented in memory of his brother, Henry W. Berg, will be used for the construction of a modern research laboratory building, and will provide the first step toward improved facilities for the institution's research work.

The new structure, to be known as the Henry W. Berg Research Laboratory Building, will enable The Mount Sinai Hospital to realize one of its basic plans for post-war development. Construction of the laboratory building will be started as soon after the war as material and labor become available. A site centrally located among Mount Sinai's existing group of eighteen buildings has been chosen.

With so many of Europe's hospitals and scientific centers destroyed, with large parts of their staffs disrupted, exiled or killed by the Nazis, America will have both the responsibility and opportunity for leadership in post-war medicine," the Hospital's Trustees declared. "Through Dr. Berg's gift, The Mount Sinai Hospital will maintain its position in the forefront of scientific research, and will be enabled to make a real contribution toward making New York City a world center of medicine."

Dr. Berg has been identified with The Mount Sinai Hospital for a half century, since his appointment there as an intern in 1894. He was the leader of a group of physicians at Mount Sinai who, about the turn of the century, started a movement to bring about specialization in surgery. He himself has long been preminent in abdominal surgery and was one of the first to operate for advanced gastric ulcer by removal of the stomach. The Trustees hailed Dr. Berg's gift "as a fitting climax to his half century of medical and humanitarian service to Mount Sinai, both as a member of the Hospital's staff and as a generous contributor to its support."

Dr. Henry W. Berg, in whose honor his brother donated the new building, is also a member of The Mount Sinai Hospital Attending Staff for forty years until his death in 1938. The two brothers were lifelong associates, not only at the hospital but also in their private interests, and maintained joint offices. They shared a hobby of collecting rare books and manuscripts, and amassed a collection which Dr. Berg in 1940 and 1941 presented to the New York Public Library, and which is now housed in special rooms there.

Plans for the Henry W. Berg Research Laboratory Building will provide accommodations for research in bacteriology, pathology, physiology, chemistry, gastro-enterology, cardiology, hematology, endocrinology, metabolism, surgery, biophysics and other branches of research. The Hospital's electron microscope, its ultra-centrifuge and other specialized research apparatus will be housed in the new structure.

"In the past, investigators at Mount Sinai have made important medical contributions despite the handicap of inadequate facilities," the Trustees state. "With the extraordinary facilities of the new building, they should be able to enlarge their contributions and increase their service to the sum of human knowledge about disease and its care."

The new building will aid another essential phase of the Hospital's work—the post-graduate training of physicians and research workers. "Mount Sinai functions as a center of education of physicians and medical research workers from all parts of the country and abroad as vital as its responsibility for the care of the sick," the Trustees stated. "For many years the Hospital's Department of Graduate Medical Education, operating in association with the College of Physicians and Surgeons of Columbia University, has rendered important service to hundreds of students, by providing essential laboratory studies. After the war, medical men not only of America but of the whole world will turn to this country for such training, since for many years to come the universities and hospitals of the Old World will not be able to provide it."

"Our medical institutions must stand ready, therefore, to help in the training of these men. On them rests the responsibility for the future health of the nation, and indeed of the whole world. Dr. Berg's gift will enable The Mount Sinai Hospital to carry its share of the community task, in keeping with its fine tradition of service."

THE GREATER MOUNT SINAI DEVELOPMENT FUND

As a result of a series of studies, the officers and trustees of The Mount Sinai Hospital have adopted plans for the enlargement of its facilities to serve community needs, and to promote medical research and graduate medical education. A fund of \$5,000,000 is required to carry out the planned development, and is now being sought.

In a few years Mount Sinai will observe its one hundredth anniversary. In its founding it has made a substantial contribution to community health and to medical knowledge. But the future holds promise for even greater service. The devastation wrought by World War II, the draft of our medical manpower, the introduction of new therapies—all these present unprecedented opportunities for educational, research and community health services. Mount Sinai will be called upon to meet these developments on a larger scale than ever before. Accordingly, the trustees have made plans involving three projects:—

I

THE MOUNT SINAI INSTITUTE OF BIOGENETIC RESEARCH AND THE MATERNITY PAVILION

When the present Mount Sinai Hospital was built, the home rather than the hospital was still the accepted place for confinement for most mothers. It is therefore understandable that those who planned the present group of buildings omitted a maternity pavilion. But today, 95 per cent of all babies in New York City are born in hospitals. No general hospital is complete which does not minister to obstetrical cases.

In Incomplete Hospital. The lack of a maternity service has been a great handicap to Mount Sinai. It has not been able to serve the community in this important field of medical care. Its interns have not been able to obtain adequate training in obstetrics and have had to seek such instruction elsewhere. Resident nurses have been sent to another institution for the requisite obstetrical work—a costly and makeshift program. Mount Sinai's gynecological and pediatric staffs have labored at a disadvantage because at the critical period of both mother and child—the time of birth—the Hospital could not provide the necessary facilities. It is vital for patients as well as for teaching and research purposes that an obstetrical service be established.

Healthier Mothers and Babies. The Hospital Development Fund envisages therefore an Institute for Biogenetic Studies, which is dedicated to the origin of life and its development, and which will include a Maternity Pavilion. When completed, it is believed that this Institute will provide even more than maternity care in the most modern and comprehensive sense. It will pioneer in clinical and biologic changes in many phases of human procreation. The pregnant woman, the development of the ovum, factors in heredity, sterility—these will constitute fields for investigation.

The new Pavilion will have a capacity of about 150 beds, including 60 ward, semi-private and 40 private beds. It will offer a continuity of treatment

during pregnancy, childbirth and the lying-in period and will train mothers in the proper care of their babies in the early months of life.

II

THE MOUNT SINAI LABORATORY BUILDINGS

Mount Sinai's record of successful medical research has been long and distinguished. The Hospital was one of the first in America to introduce antiseptics in surgery. The mastoid operation was pioneered there. The first method for determining kidney function by X-ray was made possible through the discovery by a member of the Staff of the Hospital. Physicians working in the Hospital laboratories have been able to throw much light on such conditions as coronary thrombosis, tumors of the brain and spinal cord, malignant tumors of the bone and pneumonia. The Lewisohn citrate method of blood transfusion has radically simplified the technic employed in this highly important procedure. The Schwartzman phenomenon, named for its discoverer who is in charge of the Bacteriology laboratory, opened the way to new and important methods in the preparation and testing of antitoxic serums. One of the most dramatic treatments recently developed at Mount Sinai is the five-day drip therapy for syphilis.

The Mount Sinai laboratories are known, not only for their work, but also for their workers. Many of the men trained there have continued their distinguished work in the Hospital. Others hold responsible positions in institutions all over the country.

Medical Advances Await New Laboratories. The present need for adequate laboratories is too well known and too keenly felt to require discussion. Year after year, as new medical developments have occurred, the existing laboratories and research facilities at Mount Sinai have become more and more crowded. Most of them are at present located in odd scattered spaces, badly adapted and out of date. In 1920 there were 33 laboratory workers; seven years later there were 160; today there are 250. The number of research projects has grown correspondingly. The present lack of space and the need for new types of scientific equipment render essential adequate structures where these men and others to follow may carry on their work and enlarge their contributions.

Proposed New Laboratory Buildings. The proposed buildings will house equipment consistent with an ambitious program for scientific undertakings. Modern laboratories will be built for routine examinations to guide in the application of modern therapeutic measures, for research in new medical fields and for broader training for physicians. Adequate space and equipment will also be made available for intensive investigation in bacteriology, serology, pathology, biological and physical chemistry, hematology, endocrinology, physiology and other divisions of research.

New buildings will house a million-volt X-ray machine which promises new possibilities in the treatment of deep-seated tumors. One or two floors will be devoted to Mount Sinai's Consultation Service, which gives annually to more than 3,000 families of limited means the diagnoses of specialists they could not otherwise afford to consult.

he plans include doctors' offices with all auxiliary services, which can be used by the day or hour to young physicians just entering practice. Use of the offices will also enable many of the Attending Staff to carry on their own practices without leaving the institution and more easily to supervise medical offices within the Hospital.

III

POST-GRADUATE MEDICAL EDUCATION AND ENDOWMENTS FOR RESEARCH

Training the Doctors of Tomorrow. Mount Sinai plans to use its wealth of medical material, its excellent teaching staff, its museums and libraries for more intensive post-graduate education.

At the end of the war there will be a large number of young doctors who had only an accelerated medical education and accelerated practical internships. Their war experience may have been limited to some one field: tropical medicine, to surgery, to mental therapy. Older physicians who may have specialized before joining the armed forces may wish to reorient themselves in general medicine or in some specialty. Young physicians from Europe, from America and elsewhere will turn to the New World to complete their training, since their hospitals and laboratories have been devastated, their practices liquidated, their youth diverted to war. Mount Sinai must provide facilities to meet all these new situations.

Mount Sinai plans also to enable promising young physicians to remain in the field of research through an enlarged program of fellowship grants. Many outstanding young men have been lost to science because economic pressure has forced them to go into private practice and it is hoped to enable them to continue research. Some of the young men who will receive these new fellowships will join Mount Sinai's future staff; others will return to their homes, where their work may have an appreciable influence on raising medical standards all over the country.

Present Training Facilities. The varied educational facilities of the Hospital make it today a distinguished place in medical training. Weekly surgical clinics for medical students as well as pathological and clinical conferences are attended regularly by students from the five medical schools of New York City. Its facilities for intern training are outstanding, and because of the intensive clinical experience it provides, appointment to the House Staff is the goal of many young doctors. From the hundreds of applications it receives, the Hospital is able to select the best of many well-qualified graduates. Its post-graduate medical instruction, begun in 1910 and conducted since 1923 in affiliation with the College of Physicians and Surgeons of Columbia University, has averaged during recent years a registration of close to three hundred graduate physicians annually. In 1942-43, the faculty included 121 members of the Attending Staff.

While Mount Sinai now has some of the facilities necessary to carry out a comprehensive program of medical education, it needs additional classrooms and lecture halls which can, in part, be incorporated in already existing buildings in some of the additions contemplated.

MOUNT SINAI HOSPITAL INAUGURATES PROGRAM FOR DEVELOPMENT OF POST-WAR SERVICES

COLONEL GEORGE BAEHR AND PROFESSOR ISIDORE SNAPPER ARE APPOINTED
HEAD EXPANDED CLINICAL RESEARCH AND POST-GRADUATE MEDICAL
EDUCATION ACTIVITIES

With the appointment of two physicians to full-time positions as directors of the Hospital's clinical research and medical education activities, The Mount Sinai Hospital has inaugurated a program of expansion and reorganization to prepare for post-war responsibilities.

Colonel George Baehr, former President of the Hospital's Medical Board, Clinical Professor of Medicine at Columbia University, and, until recently, Chief Medical Officer of the U. S. Office of Civilian Defense, has resumed his duties as Attending Physician to the First Medical Service of Mount Sinai and will undertake new duties as Director of Clinical Research.

Dr. Isidore Snapper, Dutch scientist, formerly on the faculties of the University of Amsterdam and the University of Peiping, and more recently Medical Advisor to the Government of the Netherlands West Indies, has been appointed Attending Physician to the Hospital's Second Medical Service and Director of Graduate Medical Education.

These appointments are the first steps toward realization of plans for a greater Mount Sinai after the war. Later developments will include enlargement of the Hospital's clinical and laboratory facilities, and the creation of a considerable number of full-time paid fellowships for promising young physicians and research workers.

Colonel Baehr comes to this task with a long record of accomplishment as a physician and medical administrator. In the early years of the First World War he served as a member of the American Red Cross Sanitary Commission, which was sent to the Balkans and Russia to combat epidemic typhus fever. After the United States entered the war, he served with the Base Hospital No. 1 of the A. E. F., the Mount Sinai Unit, at Vauclaire, France, and was Commanding Officer at the time of its return. In June 1941, Colonel Baehr was again called to active service as Chief Medical Officer of the O.C.D. and Medical Director in the U. S. Public Health Service. For two and one-half years he was in charge of all measures for protection of the health of civilians in the United States and its outlying territories against wartime hazards, and for preparations for medical care of civilian victims of air raids or other enemy action. In this connection he visited Great Britain to study the methods developed there under fire, and reported his observations in a series of addresses to physicians in various parts of the United States.

Colonel Baehr is himself a graduate of The Mount Sinai House Staff. Since 1928 he has held the rank of Attending Physician to the Hospital. By appointment of the Governor, he is a member of the Public Health Council of the New York State Health Commission. He is a Trustee of the New York Academy of

icine, the Greater New York Fund, and the Community Service Society of New York, and an honorary member of the American Hospital Association. He is co-editor of "Preventive Medicine in Modern Practice," "Convalescent Care," and "Standard Nomenclature of Diseases," a contributor to Cecil's "Textbook of Medicine," and to other medical and scientific publications.

Dr. Isidore Snapper is widely known in American medical circles, having practiced this country and lectured at medical schools here frequently over a period of many years. Dr. Snapper's scientific career began while he was a student at the University of Amsterdam in 1910, when he received a fellowship from the Imperial Cancer Research Fund in London. He worked in laboratories of the Universities of Groningen and Amsterdam until 1919, when he was appointed Professor of Propadeutic Medicine and General Pathology at Amsterdam, a post which he held for nineteen years.

In 1938 the China Medical Board of the Rockefeller Foundation sent Dr. Snapper to China, where he served as Professor of Medicine at the Peiping Union Medical College. During this period he gathered material for a book on the clinical pathology of North China.

On December 7, 1941, the day of Pearl Harbor, Dr. Snapper was arrested by the Japanese Army. For many months he was held in close custody, together with three Americans, guarded by a squad of Japanese soldiers. Late in 1942 he was exchanged for five Japanese internees.

Returning to the United States, Dr. Snapper served as a delegate of the Netherlands Government to the United Nations Food Conference at Hot Springs, Virginia early in 1943. In the same year, he went to the Netherlands West Indies on a special mission for the Netherlands Government, and later became Consultant to the United States War Department, assigned to the office of the Surgeon General of the Army in Washington, D. C. He was also Medical Advisor to the Commissioners of the Netherlands Indies, Surinam, and Curacao.

Dr. Snapper is known for his research work on the kidney, on the blood, on the endocrine glands, and on other subjects. In addition to his work on pathology in China, he has published books on diseases of the bones, Boeck's sarcoid, and regional ileitis, as well as many papers in scientific journals. He has lectured at Washington University, St. Louis, and the University of Wisconsin in 1927, at Columbia University in 1931, 1938 and 1941, at the University of Minnesota in 1940, at Harvard University in 1941, at Johns Hopkins University in 1941 and 1942, and at New York University and Long Island Medical College in 1942. He delivered a scientific address at the dedication of the Frankel Hospital in Chicago in 1927. Dr. Snapper has also lectured before the Royal Society of Medicine in London, and at many other medical institutions and gatherings here and abroad.

THE FUNCTIONS OF A DEPARTMENT OF PHYSIOLOGY IN THE MOUNT SINAI HOSPITAL

FRANKLIN HOLLANDER, PH.D.

(In connection with postwar hospital plans, Dr. Hollander was asked to prepare an outline of the functions of a department of physiology. The following is an abridgement of his report)

It is my aim to acquaint you with some of the functions of a laboratory of physiological research and its role in a large general hospital like Mount Sinai. But first, a word about the science of physiology itself. This is commonly defined as the study of how organs, tissues, and cells work in the *living* body—in other words, the mode of action of the body machinery, both in health and in disease. As such, it stands in sharp contrast to the anatomical sciences, which deal with the structures of *dead* organs and tissues rather than with the activities of living ones. Prior to the beginning of this century, the major portion of the preclinical training of a medical student was devoted to various aspects of normal and pathological anatomy, whereas physiology received but scant attention. Today, however, a student in one of the foremost medical schools of this country devotes 38 per cent of the time in his freshman year to the physiological sciences, and considerably more in his junior and senior years to the clinical aspects of abnormal physiology.

Now, why has physiology gained such an important place in the theory and practice of medicine? The answer is that most ailments involve disturbances in the functions of the human organism and the practicing physician, in order to understand the abnormalities which he encounters, must think constantly in terms of disturbed physiological action. For this reason he must understand more precisely than ever before the physics and chemistry of the body. Progress in physiological research during the last quarter of a century has been so great that many a seasoned physician finds himself far behind in his knowledge of the recent advances. Because of the lack of time, formal postgraduate study in a university department of physiology is virtually impossible for most doctors. Hence a great many of them have become increasingly dependent on the members of the physiology and physiological chemistry laboratories to make up this deficit in their scientific experience.

In order to show you how a laboratory of physiology can enter into the integrated functions of a hospital, I propose to outline the activities which our department of gastro-intestinal physiology has gradually taken on, in its growth from a one-man research laboratory in 1936 to an organization which has included at one time as many as eight physicians holding the appointment of Research Assistant. These activities may be divided into four main categories as follows:

- (1) Research on physiological problems of immediate clinical importance in the hospital.

- 2) Research on basic, long-range physiological problems stimulated by major problems of clinical medicine.
- 3) Postgraduate education.
- 4) Advisory activities.

These four groups, I believe, afford an excellent guide for the organization of the work in a department of physiology associated with any large hospital or university.

The first of these groups, including problems of immediate clinical importance, may be illustrated by the following investigations conducted by members of the laboratory staff in collaboration with members of the clinical staff during the past few years: (1) The efficacy of, and the physiological basis for, intragastric therapy for the treatment of patients with peptic ulcer—(2) A new statistical procedure for studying the results of ulcer surgery—(3) A new bioassay method for male sex hormone in urine, and its application to problems of clinical interest—(4) The effect of artificial fever on gastric secretion—(5) The insulin test for vagus nerve continuity: its development and application in the study of vagus nerve section as a surgical procedure for ulcer—(6) A synthetic predigested diet for intra-jejunal feeding in the pre- and post-operative care of certain kinds of surgical patients, and the consequences (physiological and clinical) of its use.

Such projects are usually carried out in collaboration with the head of the service or department immediately concerned with its application. The half dozen studies mentioned here represent a like number of different departments of the Hospital. Concerning the most recent of these projects—that concerned with the feeding of a predigested fluid aliment through a jejunostomy fistula—I am able to report that our new procedure has already demonstrated its efficacy in increasing the body-weight and normalizing the blood chemistry of patients with gastro-intestinal obstructions. Furthermore, our observations indicate that the method accomplishes these results without the disturbing cramps and diarrheas which have so often been reported as attending the use of other types of jejunostomy drip diet; and we are now engaged in confirming its efficacy on a suitably large series of cases. The composition of this synthetic foodstuff will be published shortly, and we expect that it will find application in other types of cases.

The second group of our laboratory activities consists of investigations also stimulated by the needs of the clinical services, but concerned with basic, long-range physiological problems. In pursuing at least one such problem simultaneously with several of the more immediate variety, I have been guided by a statement of John Dewey's that "It does not pay to tether one's thoughts to the post of usefulness with too short a rope." One of these projects is concerned with the mechanism of formation of hydrochloric acid by the stomach glands. This work was prompted by the fact that ulcer disease is one of the most common disorders of adult life, and incidentally, the chief cause of military medical disability in the present war. One authority places its incidence at 15 per cent higher—which means that one adult out of every six or seven possesses a peptic ulcer or the residual scar of one. Now, the immediate causative agent

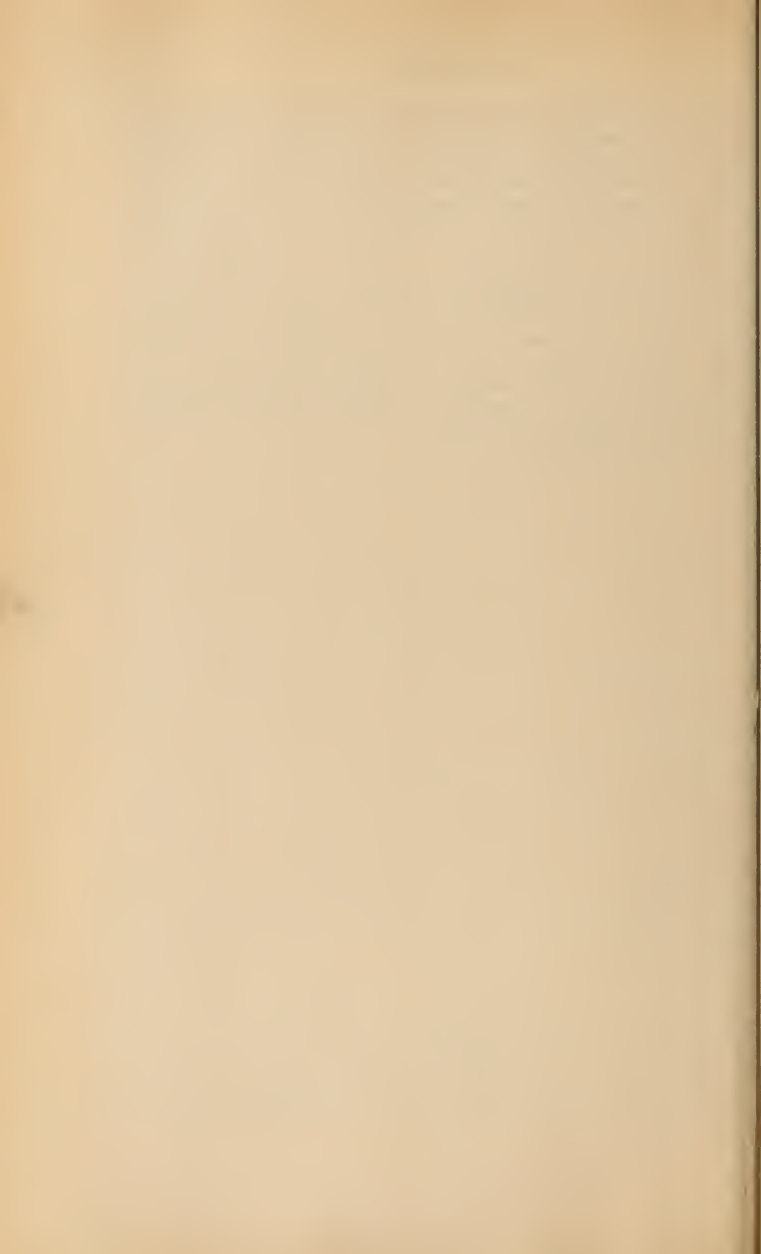
of gastroduodenal ulceration is generally recognized to include the hydrochloric acid factor of the stomach secretions. Hence, if some way can be found interfering with the organization of the gland cell which secretes this acid, sound medical treatment will have been discovered for a most vexing and costly disease. For this reason we have spent considerable time in studying the chemical, physical and cellular processes by which this acid is produced in the stomach.

Another problem of long-range character on which we are engaged at present is concerned with mucus secretion throughout the digestive tract. It is the chief function of this secretion to protect the gastro-intestinal tract against chemical and mechanical irritation, and there is reason to believe that the mucus may play a large role in relation to gastritis and gastroduodenal ulcer. Mucus secretion has an important bearing also on experimentally produced cancer of the stomach in laboratory animals. Since little is known today about the physiology of this secretion, it was felt that such an investigation, if pursued far enough, might yield important clinical data. A considerable amount of the groundwork on this problem in relation to the stomach has already been completed and is now being prepared for publication. The importance of mucus secretion as a protective agent is not restricted to the digestive tract alone, but extends to many other parts of the body. In fact, because of its possible importance in relation to the problem of human sterility, we are already engaged in a collaboration with the Gynecological Service, in a study of this secretion as it occurs in both the male and female genital tracts.

The third group of our activities is entirely educational in nature and has its origin in the fact that medicine is becoming, not less of an art, but more and more of a science. This change is especially apparent in the modern approach to disease as a form of *disturbed physiology*. . . . Since many physicians lack detailed training in physiology, and have not kept up with the rapid progress in this science, the giving of formal courses and conferences has become a major function and link between the physiologist and the clinician. The latest example of this phase of our work at The Mount Sinai Hospital is a postgraduate course in the principles of normal and pathological physiology of the digestive tract; another one is concerned with the disturbances in water and electrolyte balance associated with various diseases. Another course given by our department deals with statistical methods for laboratory workers and clinicians. We also take part in an intensive clinical course in gastroenterology given by a group of our staff members. Participation in the various conferences, seminars and surgical grand rounds on the wards is another phase of this educational program.

This brings me to the final group of our activities—advisory work for other departments of the Hospital. Sometimes this work has been related to physiological questions, either clinical or experimental. Often, it has been concerned with matters of statistical analysis or interpretation. It is noteworthy that many of the research projects on which we have collaborated with other departments of the Hospital have evolved out of these casual consultations.

The foregoing brief enumeration of the variety of tasks with which we are confronted in our laboratory gives, I believe, a clear indication of the need in the Hospital for a department equipped to handle all kinds of physiological problems. To some extent we have been able to help our colleagues, but limited space and equipment have formed insurmountable barriers to a greater exercise of these cooperative functions. Now that the removal of these barriers is in prospect, it is time to give thought to the type of organization which will be adapted to the peculiar needs of our institution. Broad principles of organization of such a physiology department must be formulated before any serious thought is given to matters of laboratory construction. Otherwise, I fear, the activities of this department may become subservient to its physical structure instead of developing freely in accordance with your vision of a new type of postgraduate medical institution. I believe that the relation of a laboratory of physiology to the medical and surgical activities of a big modern hospital is of the utmost importance today, and I hope I have conveyed to you something of my conviction in this regard.



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WALDEMAR KOPS ELECTED PRESIDENT OF THE
MOUNT SINAI HOSPITAL

Valdemar Kops, Acting President of The Mount Sinai Hospital for the past 5 years, was elected President of the Hospital on Tuesday, October 10th, at a meeting of its Board of Trustees.



WALDEMAR KOPS

Mr. Kops completes twenty years of service as an active and forceful member of the Board of Trustees of The Mount Sinai Hospital including six years as its first Vice-President.

His father, Daniel Kops, was a Trustee of the Hospital from 1913 to 1944, marking a continuity of service of thirty-one years in his family.

Mr. Kops is also a Director of the Research Council of the New York City Department of Health, a Trustee of the Baron de Hirsch Fund and a Trustee of the Federation for the Support of Jewish Philanthropic Societies of New York City, which he served for three years as Chairman of its Business Men's Council.

During the First World War, Mr. Kops served as Lieutenant-Colonel in the U. S. Chemical Warfare Service and was in charge of development of gas defense material. In this connection, he invented a new type of gas mask used for the Army.

BELA SCHICK LECTURE¹STUDIES ON THE NATURAL HISTORY OF POLIOMYELITIS²ALBERT B. SABIN³

The privilege of giving the second Bela Schick lecture is deeply appreciated because it affords me the opportunity to participate in honoring one of the foremost living contributors to that body of knowledge which forms the basis for the control of infectious diseases. The lecture tonight will be concerned with an infectious disease which we have not yet learned to control. The established immunologic and chemotherapeutic approaches to the problem presented by poliomyelitis have been explored repeatedly without success. It has become all the more important, therefore, to understand in greatest detail the behavior of the infecting virus both in the human body and away from it in nature. All the ongoing attempts to acquire such knowledge unquestionably have been inspired by the hope that if the true facts were known, one might perhaps learn how to put up barriers between the virus and the human being, or between the virus in one part of the human body where its presence does little damage and other parts where its full multiplication and spread produce the paralytic manifestations which impart to the disease its serious and dread aspects. A thorough understanding of the natural history of poliomyelitis thus requires the possession of answers to many specific questions, among which may be listed the following:

1. Where and how does the virus enter the human body?
2. What tissues does it attack and from what site or sites does it invade the central nervous system (CNS)?
3. What parts of the CNS does it affect and what is the pathologic basis for the various manifestations of the disease?
4. How is the virus eliminated from the body?
5. What are the sources of infection or reservoirs of virus in nature?
6. What factors determine the occurrence of epidemics or increased incidence of the disease during the warm seasons of the year?

Many good minds have speculated on the answers to these questions, especially since the discovery of the virus etiology of the disease about 35 years ago. These speculations have brought forth so many different hypotheses that I

¹ Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, N. Y., May 2, 1944.

² The studies discussed in this lecture were carried out in part at the Rockefeller Institute for Medical Research, New York, and since 1940 in Cincinnati with the aid of The National Foundation for Infantile Paralysis, Inc.

³ Now Major, MC., A.U.S., serving with the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, U. S. Army. On leave of absence from The Children's Hospital Research Foundation and the Department of Pediatrics of The University of Cincinnati College of Medicine.

should be very much surprised if the actual truth were not to be found among them, hidden though it may be. A rational picture of the natural history of poliomyelitis cannot be built, however, even on the most brilliant mental images resulting from speculation. This rejection of speculation and hypothesis unsupported by adequate data or experimental confirmation, reached its climax about a decade ago, and led to a reaction in which too much reliance was placed on limited observations in experimental animals. The results of extensive work with a few laboratory-adapted strains of poliomyelitis virus in rhesus monkeys led to a phase reaching its climax in 1937, during which many critical investigators believed that the answers to the questions listed above were actually at hand. It was believed then that the virus in nature was limited to man, in whom it affected chiefly the olfactory mucosa and certain parts of the central nervous system, the disease being transmitted from person to person by droplets expelled from the upper respiratory tract. Since this picture failed to account for the occurrence of epidemics during the summer and autumn months it was supplemented by the assumption that "something" happened to the host during these seasons which resulted in a higher incidence of the paralytic form of the disease. It will be recalled that this hypothesis was quickly followed by the discovery that it was possible to treat the olfactory mucosa of animals with certain chemicals in such a manner that the virus could be effectively prevented from invading the central nervous system (1). However, the inability to prevent the disease in human beings by the application of this discovery (2), was as potent a factor as any other in leading to the critical reexamination of the current image of the natural history of poliomyelitis and of the data upon which it was based.

It became clear for one thing that it was necessary to check all assumptions about the behaviour of the virus in the human body by the most detailed studies on the disease as it occurs in man. Experimental work on other neurotropic viruses in the meantime gave the clues which suggested the methods that might be used in obtaining an indication of the portal of entry and pathways of progression of the virus (3). Thus, following the demonstration in 1936, that under certain conditions the presence or absence of lesions in the olfactory bulbs of rhesus monkeys could indicate whether or not poliomyelitis virus had invaded the CNS by the olfactory pathway (4), I undertook the examination of approximately 2,000 serial sections of olfactory bulbs from fatal human cases. The failure to find any lesions in these sections (5), was, however, countered by the possibility that in human beings the virus could perhaps invade the olfactory bulbs without leaving any histopathologic evidence of its presence. At about the same time the work of Harmon (6), and especially of Trask, Vignec, and Paul (7), and others (8), established beyond doubt that the virus of poliomyelitis could be isolated with considerable frequency, if not regularly, from the stools of patients with abortive, nonparalytic, and paralytic poliomyelitis. This was countered, however, by the explanation that the virus in stools had its origin in the swallowed secretions of the upper respiratory tract, and the greater incidence of positive isolations from the stools was assumed to be the result of the concentration in the colon of virus swallowed over a period of days. This was the status of the prob-

when it appeared to me early in 1940 that a systematic search for the virus poliomyelitis in the human body had to be made, to determine whether or not distribution corresponded to any special pattern, that might point not only the site from which the virus invades the nervous system, but also to its mode spread and elimination.

These and related studies to be mentioned later were carried out in 1940, 1941, and 1942 with the invaluable assistance of Dr. Robert Ward. Necropsies were carried out by ourselves under relatively aseptic conditions and with sufficient precautions and sterile instruments to permit the dissection and handling of each specimen without contamination by virus in other tissues. The specimens were immediately frozen with solid CO_2 and remained so until preparation for inoculation into one or more monkeys. The results of tests for virus in seven cases of poliomyelitis in which all the selected tissues were studied (9) are presented in table I. It is apparent that partly due to the difficulty inherent in the transmission of human virus to monkeys and perhaps also because of the longer duration of illness in some instances, the virus was not consistently demonstrated in any one tissue. However, when the tests on all the cases are pooled, a distinct pattern of virus distribution emerges in which certain groups of tissues yield positive results with considerable regularity while others are consistently negative. Thus, in the central nervous system, the olfactory bulbs, the anterior perforated substance (a station along the olfactory pathway) together with the adjacent corpus striatum, and the anterior frontal and occipital portions of the neopallial cortex were consistently negative, while the motor cortex, diencephalon, mesencephalon, medulla and pons, and spinal cord were predominantly positive. This distribution of virus in the CNS is in good agreement not only with the known distribution of neuronal lesions, but also with the concept of the progression of virus along specific pathways and insulated tracts. In the next group of tissues one finds that the nasal mucosa, the salivary glands, the superior cervical sympathetic ganglia, the suprarenals, and the cervical and mesenteric lymph nodes were consistently negative, whether tested in rhesus or cynomolgus monkeys. The virus was demonstrated in one instance in the abdominal sympathetic ganglia of the celiac plexus in a case of primary bulbar poliomyelitis and in a pool of the lungs, liver, spleen, and kidneys as well as in a mixture of the axillary and inguinal lymph nodes of a case which succumbed within 12 hours after onset of paralysis. Next to the CNS, however, the virus was predominantly situated in the alimentary tract. The pharyngeal mucosa alone, or together with the tonsils, was positive in 4 of the 7 cases. Despite the fact that only a small portion of the entire small intestine was being tested, the washed wall of the ileum yielded virus in 3 cases and the ileum contents in two. Very significant also was the finding that the contents of the descending colon and sigmoid contained the virus in each instance while the washed wall was positive only once. The possibility that the presence of virus in the washed intestinal wall might be due to incomplete washing away of the contents was, of course, considered, but it seemed especially unlikely in the case of the ileum since a small portion of the washed wall was positive on two occasions when the total contents of the entire segment were neg-

active (see cases 3 and 6). In the the descending colon and sigmoid, however the reverse was true and the regular presence of virus in the contents suggests that virus originating elsewhere in the alimentary tract was being concentrated in the colon.

The studies on tissues obtained at necropsy were continued the following year special attention being paid to the distribution of virus in different levels of the

TABLE 1
Distribution of virus in individual cases of poliomyelitis

TISSUES TESTED	CASE NUMBER, TYPE AND DURATION OF ILLNESS						
	1 Spinobul- bar S 2.5 d.* Par. 0.5 d.	2 Bulbar S 3 d. Par. 1 d.	3 Bulbar S 3 d. Par. 1 d.	4 Bulbar S 3 d. Par. 2 d.	5 Bulbar S 4 d. Par. 2 d.	6 Bulbar S 6 d. Par. 3 d.	7 Spinobu- bar S 6 d. Par. 4 d.
1. Olfactory bulbs	0	0	0		0	0	0
2. Anterior perforated sub- stance and adjacent corpus striatum	0	0	0	0	0	0	0
3. Anterior frontal + occipital cortex	0	0	0	0	0	0	0
4. Motor cortex	P	P	0	NP	0	0	P
5. Diencephalon	P	P	P	0	0	P ^c (+)	0
6. Mesencephalon	0	P	P	NP	0	P	0
7. Medulla (+ pons)	P	NP	P	NP	0	0	0
8. Spinal cord	P (+)	P (+)	P (+)	NP	0, P, P ^c	0, NP, P ^c	0, 0, 0
9. Superior cervical sympa- thetic ganglions	0	0		0	0	0 ^c	0
10. Abdominal sympathetic ganglions	0	0	0	0	NP (+)	0 ^c	0
11. Adrenals	0	0	0	0	0	0 ^c	0 ^c
12. Salivary glands	0	0	0 (10 d.)†	0	0	0 ^c	0 ^c
13. Cervical lymph nodes	0	0	0	0	0	0 ^c	0 ^c
14. Mesenteric lymph nodes	0	0	0	0	0	0 ^c	
15. Axillary + inguinal lymph nodes	NP	0	0	0	0	0 ^c	0 ^c
16. Lungs + liver + spleen + kidneys	NP (+)	0	0	0	0	0 ^c	0 ^c
17. Nasal mucosa	0	0	0	0 (15 d.)	0	0 ^c	0
18. Pharyngeal mucosa ± tonsils	NP	P (+);	0	0	NP	P ^c	0
19. Ileum—washed wall	P	0	0, P (+)	0, 0	0	P ^c (+)	0
20. Ileum—contents	P (+)	P	0	0	0	0	0
21. Descending colon—washed wall	0	0	0	0	0	P ^c	0
22. Descending colon—contents	Empty	P	P (+)	P (+)	P	P	P

P, paralytic poliomyelitis in inoculated monkey; NP, nonparalytic poliomyelitis in inoculated monkey; 0, no evidence of poliomyelitis; c, indicates that a cynomolgus monkey was used for the test; (+), passage positive.

* S 2.5 d., total duration of illness was 2.5 day; Par. 1 d., paralysis 1 day.

† (10 d.), monkey died on 10th day.

‡ No tonsils in this case.

Reproduced from Sabin and Ward, J. Exp. Med., 73: 771, 1941.

alimentary tract, the urinary bladder, the abdominal viscera, and in cases of primary spinal poliomyelitis the abdominal sympathetic ganglia of the celiac plexus (10). The results of the entire study on the localization of virus in fatal cases of human poliomyelitis are summarized in Table II. The more extensive investigation of the alimentary tract revealed that the virus could be found in addition to the sites already mentioned, in the tongue, the wall of the duodenum

middle ileum, caecum and ascending colon, and in the contents of the stomach, caecum and ascending colon, and transverse colon, although never with the reg-

TABLE II

Summary of tests for virus in fatal cases of human poliomyelitis

ALIMENTARY TRACT	
Presence of virus unequivocally established in:	Virus not found in:
Tongue..... 1 or 2/6	Oropharyngeal washings..... 0/6
Wall of oropharynx..... 5/13*	Buccal tissue..... 0/6
Wall of duodenum..... 1 or 2/6	Oesophagus..... 0/6
Wall of ileum..... 4/13	Duodenum contents..... 0/4
Wall of caecum and ascending colon 1/4	Wall of middle jejunum..... 0/4
Wall of descending colon and sigmoid..... 1/13	Wall of transverse colon..... 0/6
Contents of stomach..... 1/6	
Contents of jejunum + ileum..... 3/13	Presence of virus equivocal in:
Contents of caecum and ascending colon..... 3/5	Wall of stomach..... 2/6
Contents of transverse colon..... 2/5	Wall of upper jejunum..... 2/6
Contents of descending colon and sigmoid..... 10/10	
CERTAIN OTHER SYSTEMS	
Virus found in:	Virus not found in:
Pool of lungs + liver + spleen + kidneys..... 1/7	Nasal mucosa..... 0/7
Pool of axillary + inguinal lymph nodes..... 1/7	Salivary glands..... 0/7
	Tracheal washings..... 0/3
	Urinary bladder..... 0/5
Presence of virus equivocal in:	Adrenals..... 0/7
Pool of spleen + kidneys..... 1/1	Cervical lymph nodes..... 0/7
Trachea..... 1/6	Mesenteric lymph nodes..... 0/6
NERVOUS SYSTEM	
Virus found in:	Virus not found in:
Spinal cord..... 10/13	Olfactory bulbs..... 0/6
Medulla + pons..... 4/7	Ant. perforated substance and adjacent corpus striatum..... 0/6
Brainstem..... 4/7	Ant. frontal + occipital cortex..... 0/6
Motor cortex..... 4/7	Superior cervical sympathetic ganglia..... 0/6
Thoracic ganglia and plexus..... 1/9	

* 5/13 = virus demonstrated in material from 5 to 13 cases tested.

ability obtaining for the demonstration of the virus in the contents of the descending colon and sigmoid. This investigation also indicated that when sufficient levels are tested, the virus may be found in some portion or other of the

alimentary tract in almost all cases of human poliomyelitis. It is of interest also that while in some instances the virus could be localized in the upper as well as the lower portions of the tissues of the alimentary tract, it was limited to the upper or lower levels in others. Thus, the finding that in a case of primary bulbar poliomyelitis, the virus may be demonstrated only in the washed walls of the duodenum and middle ileum, is especially worthy of note in the formulation of any concept concerning the pathways by which the CNS may be invaded. A study such as this, the negative results, i.e., the consistent failure to demonstrate virus in certain sites, are as important as the positive ones for the final synthesis of the picture of virus behavior in the human body. Of the negative tests obtained in the second year of this study the following are especially worthy of mention:

1. The virus could not be demonstrated in the walls of the urinary bladder in any of 5 cases, in which its presence was established in the alimentary tract.

2. The oropharyngeal washings and buccal tissues were negative in 6 cases although in some of them the virus was found in the tongue and posterior pharyngeal wall.

3. The failure to demonstrate the virus in the celiac ganglia and plexus of additional cases of primary spinal poliomyelitis, although its presence in the alimentary tract of these cases was established.

As a corollary to these studies on fatal cases of human poliomyelitis, we investigated the elimination of virus in the nasal secretions, oral secretions, urine and stools of living patients during the first two weeks of paralysis (11). This study was particularly designed to test the hypothesis that the virus in the stool represented a concentration of that swallowed in the nasal and oral secretions. The nasal secretions and expectorated material were collected separately over a period of 3 days at the end of which time stool specimens or enema returns were obtained. The results shown in Table III are in agreement with those obtained in the necropsy studies in that the nasal secretions, oral secretions, and urine were negative, while the stools alone yielded the virus.

It would be too time-consuming a task to attempt to analyze in detail the significance and meaning of the presence of virus in certain sites and its absence from others. I should like, therefore, to give you my interpretation of the results and to indicate the bearing that they have on the concept of the natural history of poliomyelitis:

1. The absence of demonstrable virus in the olfactory bulbs and anterior perforated substance in the CNS indicates that the olfactory pathway need not be affected in human beings.

2. The failure to find virus in the nasal mucosa at necropsy and in the nasal secretions during life suggests that it is not the site of virus multiplication and dissemination.

3. The absence of virus in the salivary glands at necropsy and in the oral secretions both at necropsy and during life indicates that the virus is not eliminated in the saliva, and is at least not frequently eliminated with secretions expectorated from the mouth.

4. The absence of virus in the walls of the urinary bladder at necropsy and in the urine during life, indicates that the virus is not excreted in the urine.
5. The unequivocal demonstration of the presence of the virus in the washed walls of the upper and lower portions of the alimentary tract, suggests that these tissues are the source of the virus in the stools.
6. The unquestionable presence of the virus in the walls of the alimentary tract raises the following important questions—is the virus there as a result of:
 - a) secondary or centrifugal spread from the CNS which might originally have been invaded by virus from another site,
 - b) secondary localization of virus from the blood stream, or
 - c) primary entry by way of the mouth with subsequent invasion of the tissues at various levels of the alimentary tract?

If poliomyelitis virus in man spread centrifugally from the central nervous system, the way rabies virus does in man, according to corollary studies which we have carried out, or other neurotropic viruses in certain experimental animals, should have been found in the adrenals, salivary glands, urinary bladder, su-

TABLE III

Excretion of virus during the first 2 weeks of human paralytic poliomyelitis

MATERIAL TESTED	NO. OF SPECIMENS (PATIENTS)	NO. POSITIVE	ROLE OF AGE OF PATIENT—NO. POSITIVE	
			5 yrs. and under	Over 5 yrs.
Stool or enema returns.....	23	9 (39%)	7/11* (64%)	2/12* (17%)
Nasal secretions 3 days.....	22	0	0/11	0/11
Salivary secretions (saliva) 3 days.....	20	0		0/20
Urine (35-200 cc.).....	12	0		

* χ^2 with Yates adjustment for small numbers = 3.29. P is between 0.10 and 0.05.

Reproduced from Sabin and Ward, *J. Exp. Med.*, 74: 519, 1941.

prior cervical sympathetic ganglia, etc., as well as in the walls of the alimentary tract. The consistent failure to demonstrate the virus in these tissues in the human cases constitutes strong evidence against this assumption. While the case against secondary localization from the blood stream is not as clean-cut as that against the centrifugal spread from the CNS, I find it difficult to accept it on the basis of the human data because it requires the assumption of a selective affinity of the virus for the alimentary tract—otherwise why should it not be demonstrable with equal ease in the adrenals, the nasal mucosa, the urinary bladder, the salivary glands, the lymph nodes, etc. The finding of virus in exceptional instances in certain lymph nodes or in a pool of viscera or even in the blood in early cases, is not in itself evidence that the virus is first in the blood and then localizes elsewhere. Observations on many other viruses indicate that during the period of active multiplication in certain tissues, varying amounts of virus may be liberated into the blood stream. While it is always wise not to make ultimate decisions when the slightest reasonable doubt may exist, it is, nevertheless, worth noting that the observed data fit best the hypothesis which assumes that the virus

entered by mouth and then localized in one or more sites along the alimentary tract.

These findings in human beings gave added importance to the question whether or not poliomyelitis virus could readily produce the disease by the oral route, and if it did, by what pathways was the virus distributed and how did the final picture compare with that observed in man. The earlier observations of Kling and his co-workers (12), on the production of poliomyelitis in an occasional cynomolgus monkey by feeding of the virus were regarded as inconclusive because there was no evidence that infection under those conditions had not occurred by the olfactory pathway. In 1939, Vignee, Paul and Trask (13) and Burnet, Jackson and Robertson (14) first offered suggestive, although not altogether conclusive, evidence that cynomolgus monkeys could be infected by the oral route without involving the olfactory pathway. It was not until 1940, however, that Howe and Bodian (15) established that chimpanzees, whose olfactory tracts had been severed, could develop poliomyelitis after being fed human stool containing the virus. Since we were interested in determining not only whether or not infection was possible by the oral route, but also what paths the virus followed and where it localized in the normal animal, we did not interfere with the olfactory apparatus by either chemical or surgical means. Fifteen cynomolgus monkeys received by mouth a total dose of 10 to 20 cc. of virus of recent human origin ("Per." strain) inside a banana and by pipette. Six developed clinically and pathologically typical poliomyelitis, and were sacrificed at intervals of less than 1 to 3 days after onset of paralysis for study in the same manner as that employed in the fatal human cases. Before proceeding to an examination of the results of that investigation it is worth noting that the highly virulent monkey passage "M.V." virus failed to produce poliomyelitis in the 5 cynomolgus monkeys which received it by mouth by the same technique that was used in feeding the "Per." virus of recent human origin. This would suggest, a) that the olfactory mucosa is not readily contaminated by this technique of feeding, since the "M.V." virus produces poliomyelitis in cynomolgus with great ease after nasal instillation, and, b) that this result taken together with previous failures to infect cynomolgus with "M.V." virus by the oral route (notably the experiments of Flexner (16) and of Clark, et al. (17)) indicates that successful infection by mouth depends as much, if not more, on the strain of virus used, as on the host.

Among the 6 paralyzed cynomolgus monkeys, 4 had no lesions of any kind in the olfactory bulbs while 2 showed evidence of either neuronal or meningeal involvement. Detailed studies on the distribution of virus (18a) were made in the 2 monkeys which exhibited these lesions and in 3 which did not. Since it will be shown later that the virus was present in the blood of some of these monkeys, we should like to state here that the animals were thoroughly bled out before the tissues were removed. When we examine first the findings in the nervous system the following points are especially worthy of note:

1. The cerebrospinal fluid (obtained by cisternal puncture just before the monkeys were sacrificed) exhibited a rather marked pleocytosis varying from 170 to 1,250 leukocytes per cu. mm. but did not contain any virus.

2. In the monkeys without olfactory bulb lesions, no virus was found in the olfactory bulbs, anterior perforated substance and contiguous corpus striatum, and the pool of anterior frontal and occipital portions of the neopallial cortex.

TABLE IV

Localization of virus in cynomolgus monkeys paralyzed after infection by oral route

SYSTEM	VIRUS FOUND	VIRUS NOT FOUND
Nervous	Spinal cord + medulla..... 5/5	Cerebrospinal fluid..... 0/4
	Mesencephalon..... 4/5	Ant. perforated substance and adjacent corpus striatum.... 0/5
	Diencephalon..... 2/5	Ant. frontal + occipital cortex 0/5
	Motor cortex..... 4/4	Sup. cervical sympathetic ganglia..... 0/5
	Olfactory bulbs..... 1/6	Celiac plexus and ganglia..... 0/5
Alimentary tract	Oropharyngeal washings..... 3/5*	Stomach—washed wall..... 0/3
	Buccal tissue..... 4/5	Stomach—contents..... 0/2
	Tongue..... 4/5	
	Wall of oropharynx..... 2/5	
	Wall of oesophagus..... 3/5	
	Wall of duodenum..... 1/3	
	Wall of jejunum and ileum... 2/5	
	Wall of caecum and ascending colon..... 1/3	
	Wall of descending colon and sigmoid..... 1/5	
	Contents of jejunum and ileum..... 4/5	
	Contents of caecum and ascending colon..... 3/3	
	Contents of descending colon and sigmoid..... 2/4	
Lymphatic	Tonsils..... 4/5	Mesenteric..... 0/5
	Cervical..... 2/4	
	Inguinal..... 2/4	
	Axillary..... 1/2	
Others	Blood (pool of 3)..... 1/1	Blood from individual monkeys 0/2
	Liver + spleen + kidneys... 3/5	Lungs..... 0/4
	Kidney..... 1/1	Adrenals..... 0/5
	Spleen..... 1/1	Salivary glands..... 0/5
	Urinary bladder..... 2/2	
	Nasal mucosa..... 1/4	
	Trachea..... 1/5	

* 3/5 = virus demonstrated in material from 3 of 5 monkeys tested.

3. Virus was found in the olfactory bulbs of only one of the two monkeys with bulb lesions. The absence of virus in the other may be due to the fact, either that the lesion consisted only of an extension of meningeal infiltration or that it

was present only in the small piece removed for histological examination and in the remainder of the bulb. It is noteworthy, however, that in neither case was virus found in the anterior perforated substance, which may suggest that even in these two animals invasion of the other parts of the CNS might not have been by the olfactory pathway.

I should like to digress here to point out certain modifications in the interpretation of the significance of olfactory bulb lesions in monkeys infected with poliomyelitis virus of recent human origin. Using the monkey-adapted "M.V." virus in rhesus monkeys it was established that following peripheral inoculation olfactory bulb lesions were indicative of invasion by way of the olfactory mucosa and occurred only under the following circumstances: a) invariably after nasal instillation, b) occasionally after intravenous injection of large amounts of virus with ensuing elimination on the nasal mucosa, c) but not after subcutaneous, tonsillopharyngeal (18), intraocular or intrasciatic (19) inoculation and not after intracerebral inoculation except when the inoculum was close to the olfactory pathway. Using the "Per." virus, however, we have found typically severe lesions in the olfactory bulbs of 3 of 8 cynomolgus monkeys as well as in one rhesus monkey inoculated intracerebrally and intraperitoneally. The fact that following peripheral inoculation of certain strains of recent human origin the virus might get into the blood stream may, perhaps, account for this manifestation.

4. To return to the nervous system of the cynomolgus infected by the oral route one should especially note that the motor cortex had virus in each instance.

5. The consistently negative tests with the superior cervical sympathetic ganglia and with the celiac plexus and ganglia suggest:

- a) that these sympathetic pathways were not utilized for the centripetal spread of the virus into the CNS, and
- b) the lack of centrifugal spread of virus into these peripheral collections of nerve cells.

6. The essential similarity of the pattern of virus distribution in the nervous system in human beings and in these cynomolgus infected by the oral route again emphasizes that unlike certain other neurotropic viruses, such as those of rabies and encephalitis, which spread diffusely through the CNS as well as peripheral poliomyelitis virus has a tendency to remain more localized.

When we next examine the distribution of virus in the tissues and contents of the alimentary tract, we find an involvement that is much more extensive than that observed in human beings. The presence of virus in the oropharyngeal washings, the thoroughly washed buccal tissue, tongue, posterior pharyngeal wall and oesophagus of these monkeys 6 to 9 days after the last feeding of virus strongly suggests that the virus probably multiplied in these tissues. This impression gains particular strength from our knowledge that in the absence of multiplication, virus persists for but a very short time on a mucosa with which it merely comes in contact. Thus, in previous experiments (20) it was found that after nasal instillation of at least about 1,000 minimal cerebral doses of "M.V." virus in rhesus monkeys (which regularly produced paralysis in them), no virus could be demonstrated in the nasal mucosa even only a few hours later. Future

restigation, however, should supply the evidence required definitely to establish whether or not poliomyelitis virus multiplies in these tissues of the alimentary tract, and at what stage relative to multiplication of the virus elsewhere in the body. It may be noted that with the exception of the wall of the stomach the virus was found with varying frequency in the tissues of all levels of the alimentary tract.

The tests on the lymph nodes, viscera and other tissues of the same monkeys applied some additional surprises, and findings which were at variance with the results obtained in human beings. The virus was demonstrated in the tonsils (thoroughly dissected out and free of pharyngeal tissue) of 4 of the 5 monkeys and in the other cervical lymph nodes of two, but surprisingly enough not in the mesenteric nodes of any of them. Virus was also found in the inguinal and axillary lymph nodes and interestingly enough in the very two monkeys whose descending colon and sigmoid contents were also infective. The most unexpected result was the finding of virus in the blood, pool of the liver, spleen and kidney, and in the kidney and spleen individually, as well as in the urinary bladders of the monkeys without olfactory bulb lesions, which incidentally also succumbed within 6 to 12 days after the first feeding. The viruses obtained from the blood, kidney, and spleen were proved to be poliomyelitic by the clinical and pathologic picture produced in monkeys on passage, and by the negative results obtained in mice, guinea pigs and rabbits. Furthermore, these results were obtained at a time when we were isolating our test monkeys, because we realized the danger of possible cross infection among susceptible animals eliminating virus in their excreta. It is further interesting to note that the virus was not found in a single instance in the adrenals, salivary glands, and lungs, although it was present in the trachea in one case, and the nasal mucosa was positive in the one monkey whose olfactory bulbs also contained the virus.

The findings in the virus distribution study on five of the orally infected cynomolgus monkeys may be summarized as follows:

1. The virus was localized in all levels of the alimentary tract (with the possible exception of the stomach) but was demonstrable with especial regularity in the tissues of the mouth, tongue, pharynx, and oesophagus.

2. In the CNS the virus was present only in certain special regions. Its distribution therein is compatible neither with an indiscriminate spread across the blood vessels, nor with an invasion of the medulla and spinal cord by way of the olfactory pathways, but resembles rather the pattern of an ascending progression following primary invasion of the spinal cord or medulla by way of the regional nerves.

3. During the paralytic stage the virus was present in the blood, the spleen, kidney (probably also liver), the urinary bladder, the tonsils, in some instances in the cervical, inguinal, and axillary lymph nodes, and in one instance each in the nasal mucosa and trachea, but not in the lungs, adrenals, salivary glands, mesenteric lymph nodes, or cerebrospinal fluid. (This may be contrasted with the behavior of equine encephalomyelitis in the monkey, where the virus is present in the blood, but not in the cerebrospinal fluid *before* involvement of the nerv-

ous system, but is absent from the blood and present in the cerebrospinal fluid after CNS signs appear (21).)

It is not clear from the data available at the present time:

- a) whether this particular localization in the alimentary tract is peculiar to infection by the oral route or is secondary to general "blood stream infection";
- b) whether the virus is present in the blood early after feeding before it is localized and multiplied in the alimentary tract or nervous system, or as late as an "overflow" from these foci;
- c) whether the virus localizes (and multiplies?) in the spleen, kidneys, a urinary bladder early either before, simultaneously with, or after its establishment in the alimentary tract;
- d) whether localization of virus in the lymph nodes is the result of drainage from tissues infected with or contaminated by the virus, or of deposition from the blood stream.

Centrifugal spread of virus from the CNS is the least likely mechanism by which this particular pattern of virus distribution may be produced. We were unable to find any virus in the descending colon and sigmoid contents of 3 paralyzed cynomolgus monkeys infected with the same "Per." virus by the intracerebral route (19). On the other hand, Trask and Paul (22) and more recently Minick (23) observed that virus may be found in the stools of an occasional monkey inoculated intracutaneously and subcutaneously with virus of recent human origin. These observations indicate that a good deal more needs to be learned about the pathogenesis of infection produced by various strains of poliomyelitis virus in various hosts. Although we shall never be justified to transpose categorically the events observed in any one experimental animal (be it mouse, chimpanzee) to man, we may, nevertheless, expect to gain a better insight into what the virus may be doing in man, and how the end results seen at necropsy could be brought about.

The data discussed up to this point have shown how we have had to modify our concept of the behavior of poliomyelitis virus as a result of studies on human beings and on strains of recent human origin in animals. Next, I should like to review some histopathologic studies on animals infected with recent strains of virus, which have given us a new insight into the pathologic basis of certain forms of nonparalytic, mild, and transitory paralytic manifestations encountered in poliomyelitis (24). The desired information obviously could be derived neither from a study of fatal human cases nor from studies on the experimental disease resulting from infection with highly virulent monkey-adapted strains of virus which produce a prostrating paralysis. The latter type of virus attacks the majority of susceptible cells in the manner shown in fig. 1, i.e., a rapid progression through the stages of chromatolysis with acidophilic intranuclear inclusion formation to complete acidophilic necrosis and neuronophagia. However, when rhesus monkeys are inoculated with strains of human or recent human origin, a relatively high incidence of nonparalytic, mild paralytic and transitory paralytic poliomyelitis is encountered. In such animals it was found that under certain conditions, which we do not as yet understand, the host may achieve an equilibrium with the

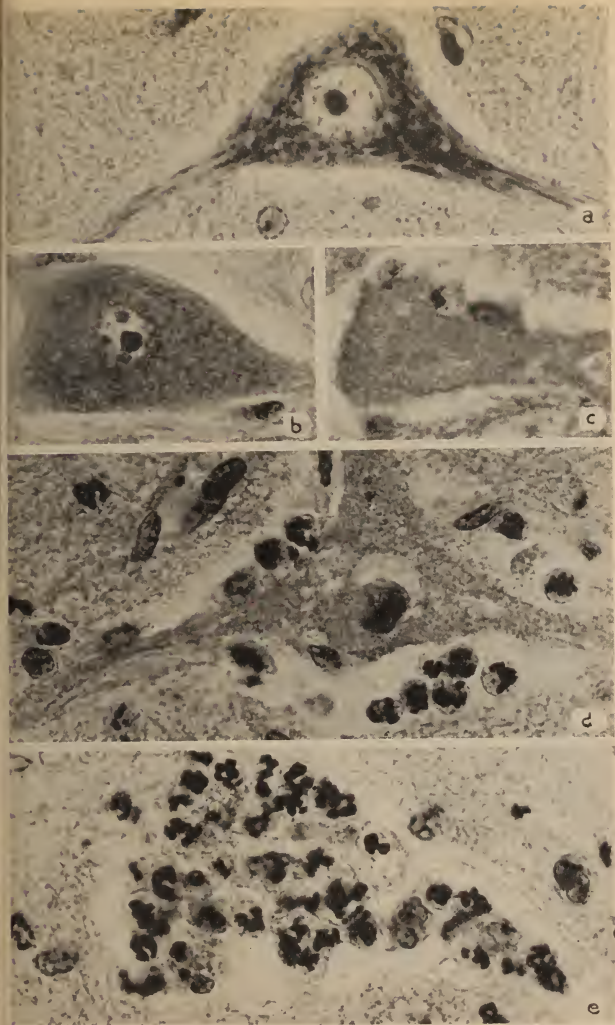


FIG. 1. Fate of anterior horn cell attacked by highly virulent "M.V." poliomyelitis virus: a, essentially normal cell; b, chromatolysis and acidophilic, intranuclear inclusions; c, complete acidophilic necrosis; d, polymorphonuclear leukocytes invading necrotic cell; e, neuronophagia by polymorphonuclear leukocytes. $\times 1,000$. Photomicrograph originally appeared in the *Journal of Experimental Medicine* (24).

virus before a sufficient number of nerve cells is destroyed to produce paralysis and that monkeys certainly do not need all their anterior horn cells for apparent normal function. Figure 2a shows the upper lumbar cord of a monkey with nonparalytic poliomyelitis killed about 10 to 14 days after a probable acute episode. Extensive lesions can be seen in the anterior and lateral horns with considerable

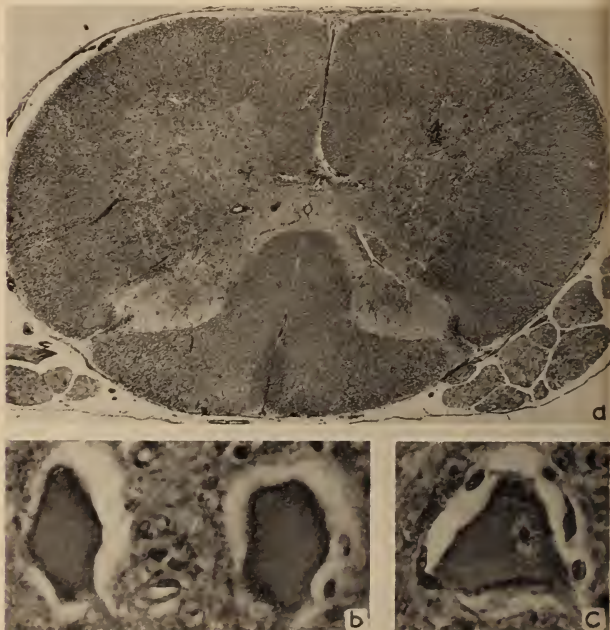


FIG. 2. Upper lumbar cord of monkey with nonparalytic poliomyelitis killed ten to fourteen days after probable acute episode: a, note perivascular and interstitial cellular infiltration in anterior and lateral horns, where a loss of some neurons and degeneration of others are evident under higher magnification; $\times 19$. b and c, anterior horn cells showing degenerative changes in the form of margination of Nissl substance and eccentricity of nucleus; $\times 640$. These photomicrographs appeared originally in the *Journal of Experimental Medicine* (24).

focal and diffuse cellular infiltration in the areas of outfall of cells. Under higher magnification (figs. 2b and c) the majority of the remaining anterior horn cells show signs of degeneration in the form of margined Nissl substance and eccentric nuclei, with only minimal signs of degeneration in the nerve roots at this stage. In monkeys killed at later stages one can find complete destruction of outfall of cells in most of an anterior horn at certain levels together with a pronounced reaction of degeneration in the corresponding nerve roots (fig. 3). While

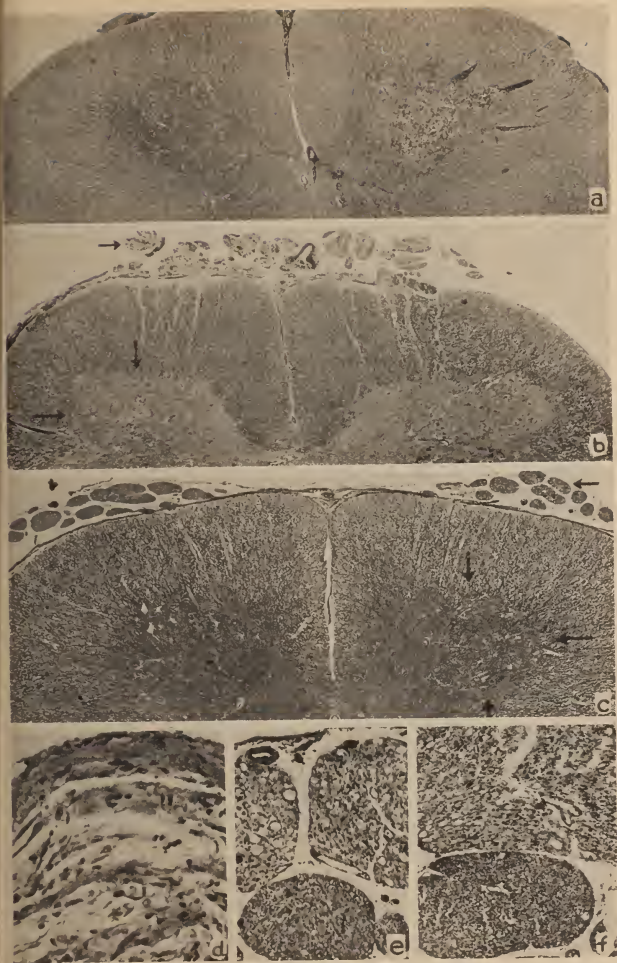


FIG. 3. Disappearance of neurons in anterior horns of monkeys with non-paralytic poliomyelitis: a, destruction of most of the right anterior horn; $\times 16$. b and c, arrows point to extensive outfall of neurons with little or no inflammatory reaction at local site in monkeys killed at later stages; $\times 20$. d ($\times 270$), e ($\times 103$), f ($\times 68$), reaction of degeneration in corresponding nerve roots; the roots in the lower portions of e and f are normal. The photomicrographs appeared originally in the *Journal of Experimental Medicine* (24).

no muscle tests to detect localized weakness were carried out on these monkeys their activity could not be differentiated from that of normal animals. The findings may be interpreted as indicating, 1) that even when actual destruction of lower motor neurons occurs, the segmental distribution of the lesions may be so spotty as not to affect the major innervation of a given muscle, and, 2) that virus need not necessarily destroy all the affected neurons but may also produce only partial degenerative changes from which recovery is possible. A similar situation probably obtains in the instances of spontaneous recovery from infantile paralysis. Monkeys were studied whose paralysis disappeared in as short a time as 12 to 48 hours after onset. When such monkeys were killed several days after apparent recovery, one could still find the virus in their spinal cord, and side by side with older glial foci of neuronophagia there were still present cells with chromatolysis and acidophilic intranuclear inclusions. Figure 4a shows the anterior horn of the lumbar cord of a monkey which spontaneously recovered from paralysis of both lower extremities. Under higher magnification one can see that only a few essentially normal appearing neurons (fig. 4b) are present and that most of the others exhibit chromatolysis and acidophilic, intranuclear inclusions (fig. 4c and d), and that some of the cells had been completely destroyed as indicated by the glial foci of neuronophagia (fig. 4e).

I should like next to fit together the various pieces of this jigsaw puzzle in some sort of picture of the behavior of poliomyelitis virus in man—a picture that may, and undoubtedly will, be modified as new pieces appear. This picture which must of necessity be incomplete, is, nevertheless, worth constructing in order that we may not only have something to shoot at, but also to obtain some idea of the probable outlines of the missing pieces. In this working hypothesis (see schema in Table V) we might assume that in most instances the virus enters the body by way of the mouth on food, fingers, etc., and that in nonimmune individuals it then localizes and ultimately multiplies in one or more levels of the alimentary tract. In perhaps the minority of individuals it then invades the spinal cord or medulla, or both, via the regional nerves, and one or another of the following events may ensue: 1) sufficient neurons may be quickly affected to give rise to severe paralysis, 2) mild or transitory paralysis may result when the process is halted before too many neurons are irreversibly damaged, or 3) insufficient multiplication of the virus may occur to produce any significant or apparent signs of involvement. In the last instance the virus might either disappear from the nervous system after a brief interval, or else remain there quiescent in equilibrium with the host. Enough circumstantial evidence is available to suggest that such an equilibrium may perhaps be upset by severe exertion and a variety of other as yet unknown factors, with the result that what might otherwise have remained an inapparent infection is converted into the paralytic form of the disease. It is not improbable that in the majority of individuals, for reasons as yet unknown, the virus might not invade the CNS after localization in the alimentary tract and there may be few or no clinical signs of its presence. In this instance also, it may remain in the alimentary tract for shorter or longer periods in the quiescent form, except when tonsillectomy, adenoidectomy, dental operation

and other, as yet unknown, factors open the gates for invasion of the CNS and development of the paralytic disease. Whatever course is taken, and while there may occasionally be an overflow of virus into the blood, viscera, and certain lymph nodes, the virus is excreted predominantly by way of the stools.

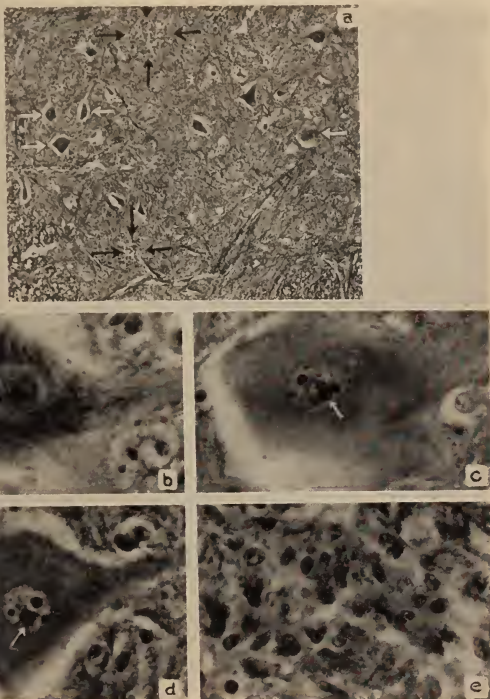
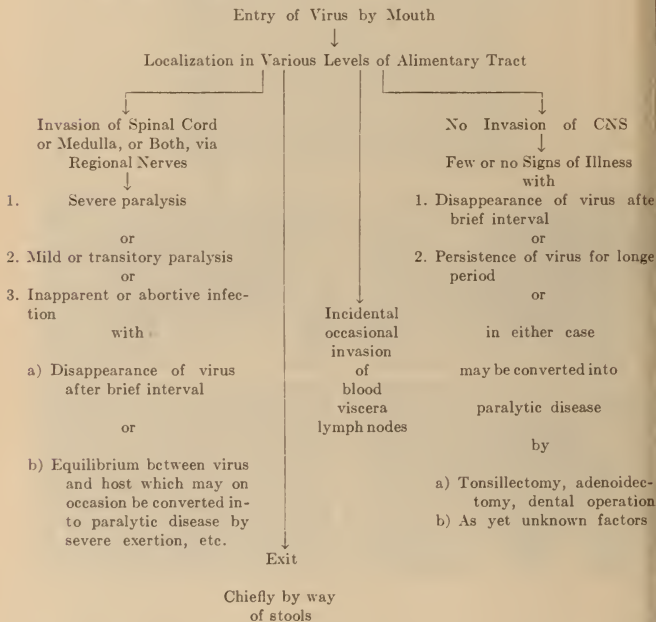


FIG. 4. a, anterior horn of monkey killed two days after spontaneous recovery from paralysis of lower extremities. Black arrows point to glial foci of neuronophagia (c and d); $\times 68$. b, one of two almost normal neurons in section; $\times 640$. c and d, cells showing chromatolysis and intranuclear inclusions; arrows point to basophilic nucleoli, while the other sharply outlined, intranuclear bodies are the inclusions; $\times 640$. e, focus of neuronophagia made up chiefly of glial cells, $\times 640$. The photomicrographs appeared originally in the *Journal of Experimental Medicine* (24).

Even if time should prove this picture of the behavior of poliomyelitis virus in man to be correct, it would tell only part of the story of the natural history of poliomyelitis. For example, we do not know the mechanism by which the major-

ity of individuals infected with poliomyelitis virus escape the paralytic form of the disease, and we also do not know the factors which are responsible for the increased incidence or epidemics during the summer and autumn months. The last part of this lecture will be concerned with studies designed to elucidate the latter problem. The tremendous amount of work which had been done by many investigators on the presence of the virus in stools and the consequent demonstration by Paul and Trask, et al. of its presence in sewage (25), naturally raised the

TABLE V
Working hypothesis of behavior of poliomyelitis virus in man



question as to whether or not some other host might pick up the virus so widely disseminated in nature by human beings. It required no special insight to select the nonbiting, filth flies for the initial intensive investigation. The two most extensive studies were carried out in 1941 by Paul and Trask, et al. (26), and by ourselves (27). The former investigators trapped their specimens in rural areas and 3 of their 4 positive virus isolations were obtained from flies caught within a few feet or yards of a potential source of virus in the form of exposed, recently

vacuated human feces. We trapped our flies under totally different conditions, in two large cities, Atlanta, Ga., and Cleveland, O.,—during the course of fairly large outbreaks of the disease. Our procedure was to visit the homes of patients who had been admitted to the hospital several days or even weeks earlier, and set out a freshly-baited, clean fly trap of the type shown in figure 5 in the yard, usually quite close to where the garbage was kept. With one possible exception no positive results were obtained in areas in which exposed human fecal matter was not in evidence, there were no privies, the patients were away in the hospital, and the other probable virus carriers in the homes used good flush toilets. It



FIG. 5. Flies collected with meat bait during a 24 to 48 hour period in one back yard during poliomyelitis epidemic in Cleveland in 1941. Poliomyelitis virus was demonstrated in a small sample of these flies.

appears to us all the more significant, therefore, that in tests on 15 different collections of flies, the presence of poliomyelitis virus could be demonstrated in 8. An analysis of the results shown in Table VI reveals a number of points that are specially worthy of note:

1. The flies which had been frozen for several months, were washed in water and the decanted washings were instilled intranasally; the flies, themselves, were ground up in water to form a 10 per cent suspension, and the etherized, centrifuged supernatant liquid was injected intraperitoneally while the untreated sediment was fed by mouth.

2. Among the 8 monkeys, which exhibited poliomyelitic changes in the spinal cord, only 2 had lesions in the olfactory bulbs. If the untreated fly washings were the chief source of the virus, or indeed had any virus at all, the olfactory bulbs should have been regularly involved. The fact that they were not affected would tend to suggest, therefore, that most of the virus was probably within the flies.

3. All the positive results were obtained in cynomolgus monkeys, which was also the experience of Paul and Trask. Four of the positive collections were also inoculated into 4 rhesus monkeys, but with negative results.

4. In 5 of the 8 positive tests distinct paralysis, either of the extremities or only of the face, was present in the inoculated monkeys, and typical poliomyelitis with paralysis of the upper and lower extremities was obtained on passage into new cynomolgi. In the other 3 instances, there was no definite paralysis, but poliomyelitic lesions were present in the spinal cord; however, since the monkey

TABLE VI

Detection of poliomyelitis virus in nonbiting flies trapped in cities during epidemics

Flies washed in water—decanted washings instilled intranasally

10% suspension in water centrifuged (etherized supernatant liquid intraabdominally
untreated sediment by mouth)

	CLEVELAND	ATLANTA	TOTAL
No. of areas sampled and tested.....	12	3	15
No. considered positive for poliomyelitis virus.....	7	1	8
No. of samples produced paralysis in first monkey—			
Facial only.....	2	1	3
Extremities.....	2	0	2
No. of samples produced paralysis on passage—			
Extremities.....	4	1	5
No. of monkeys with lesions in spinal cord exhibiting lesions			
in olfactory bulbs.....	2/7	0/1	2/8
Positive results in cynomolgus monkeys.....	7/14	1/3	8/17
Results in rhesus monkeys.....	0/7		0/7

were sacrificed a month or longer after inoculation no virus was obtained on passage. Suitable studies on other hosts indicated that these viruses fulfilled the criteria for the identification of a poliomyelitis virus.

5. The flies caught in Cleveland, where fresh meat bait was used, were predominantly blowflies (especially *Phaenicia sericata*), while more than 95 per cent of those trapped in Atlanta with sugar and banana bait consisted of ordinary house flies (*Musca domestica*) (27b). Virus, however, was isolated from collections in which either one or the other type of fly predominated.

The flies which thus far have been found to harbor the virus are of the variety that feed on excreta and decayed matter and are most likely to transmit the virus by contamination of food. The high incidence of virus isolations from flies caught even in some of our cleanest and most sanitary urban areas cannot be dismissed as an incidental finding without epidemiologic implications. I must mean that at some time or other, somewhere in the vicinity within a radius of one or more miles, they must have had the opportunity to pick up the virus

While the important question of whether or not the virus undergoes multiplication in these flies still remains to be investigated, it is, nevertheless, clear that as long as myriads of flies have the proven capacity to transport the virus and the obvious capacity to contaminate human food with it—and in view of the fact that the possibility of infection with poliomyelitis virus by way of the mouth is now established beyond doubt, it is very difficult indeed not to visualize the important role that flies may play in the dissemination of the virus during the summer and autumn months. We know now that, unlike the summer encephalides of man, which are transmitted by biting insects—the mosquitoes, the occurrence of poliomyelitis is not limited to any one season. We have isolated the virus from people with the paralytic, nonparalytic, or inapparent forms of poliomyelitis during the middle of a very cold winter in Ohio (27b). While it is thus clear that the infection can be perpetuated and disseminated in the absence of insects, it is also not improbable that the greater dissemination of the virus, made possible through the agency of myriads of flies during the summer and autumn months, may account for the seasonal character of poliomyelitis outbreaks.

In my opinion, we are only at the beginning of the trail in this approach to the problem. The work on the possible role of flies in the causation of epidemics of poliomyelitis requires extensive elaboration. *Cynomolgus* monkeys have unfortunately not been available since the Japanese entered the war, and many attempts by several investigators in the last two years to isolate virus from flies by inoculation of rhesus monkeys have been uniformly unsuccessful. Just as soon as *cynomolgus* monkeys or other equally suitable experimental animals are again available, we shall have to begin this work all over again—and at the same time that the nonbiting flies are more thoroughly investigated, we shall have to search just as hard among the various biting insects, mammals and birds that may be found in epidemic areas, to establish as unequivocally as possible what role, if any, they may play in the dissemination of the disease.

For more than 2 years now I have done no work on poliomyelitis. I have been an interested observer from the sidelines and I have heard it said that poliomyelitis investigation has gotten into a rut of flies and feces. Several years ago a great man said that we have only just begun to fight—we may paraphrase him by saying that we have only just begun to learn.

Before concluding this lecture, I must confess to certain misgivings about my presentation tonight. I have drawn largely on my own studies on the natural history of poliomyelitis and may have left the impression that very little other work has been done on the subject that is worth mentioning. Perhaps I may tell you a story of how the famous Prof. Szent-Györgi behaved when he was confronted with a similar difficulty. He was invited by a famous Institute to give a seminar, and after talking for over an hour about certain problems in oxidation-reduction illustrated chiefly by his own studies, he invited discussion. Whereupon one of the members of this Institute proceeded to relate his own very pertinent observations on the subject. Prof. Szent-Györgi was obviously embarrassed and when his turn came to speak, he said: "Prof. X's numerous observations are, of course, of the greatest importance to the subject of oxidation-reduction and are well known, but if I had taken the time to describe his many

contributions, I should have had no time left to tell of my own." Similarly if had taken the time to mention all the interesting observations having a bearing on the natural history of poliomyelitis made in recent years by Howe, Bodian, Trask, Paul, Kessel, Faber, Francis and others, I should have had no time to tell about my own.

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HODGKIN'S DISEASE OF THE SKIN¹

OSCAR L. LEVIN, M.D., AND HOWARD T. BEHRMAN, M.D.

[New York]

A wide variety of cutaneous manifestations have been grouped under the heading of the lymphomatoid diseases of the skin. These diseases have been further subdivided into the leukemias, the reticuloses, granuloma fungoides, lymphosarcoma and Hodgkin's disease.

The skin phenomena which occur in Hodgkin's disease may be placed in one of two groups. Those in the first group are the more common and consist of non-specific lesions which are neither histologically nor clinically pathognomonic of the disease. Of their symptoms, itching is the most frequent. It may be extremely intense and unaccompanied by any changes whatsoever in the skin. It is sometimes associated with a mild or severe type of erythroderma or exfoliative dermatitis. Urticaria of both the simple and the papular types, is not infrequently observed. Cole placed the order of frequency of signs and symptoms in Hodgkin's disease as follows: diffuse exfoliative dermatitis, pruritus, prurigo-like eruptions, urticaria, edematous swellings, pigmentation, outbursts of perspiration, alopecia, dryness of the skin, icterus, purpuric lesions and tumors of the skin.

The second group of lesions encountered in Hodgkin's disease are those which show the specific and pathognomonic histologic characteristics of the disease in the skin. This group is comparatively rare. The lesions are usually tumors or plaques. Fox reported a case presenting tumor-like infiltrations in the scalp and on the forehead. In some instances, a generalized erythroderma has been reported. The cutaneous findings do not occur at any specific period of the disease. They may antedate the general symptoms and signs or occur concurrently with them. In the patient reported in this paper, the cutaneous lesions did not appear until several years after the diagnosis had been established.

CASE REPORT

History. H. G., (O.P.D. #41-5385) a 32 year old negro, was admitted to The Mount Sinai Hospital in September, 1941 complaining of progressive swelling of the left side of the neck of three months' duration. The swelling interfered with motion of the neck and was associated with a fifteen pound loss of weight. There was no cough, bleeding tendencies, diarrhea or cutaneous eruption.

Examination. The patient was a well developed and nourished colored man, in no distress. The pupils were round, regular and reacted to light. The fundi were normal. The left and right supraclavicular lymph nodes were enlarged, matted together, firm and fixed. They were not tender and showed no evidence of an underlying inflammatory process. The configuration of the chest was normal. There was some widening of the mediastinum detected on percussion. The heart sounds were of good quality and the blood pressure was 50 systolic and 75 diastolic. The abdomen was soft and no mass or viscera was palpable.

Laboratory data. Blood: hemoglobin, 86 per cent; white blood cells, 13,000 with 74 per cent segmented polymorphonuclear leucocytes; 16 per cent non-segmented polymorpho-

¹ From the Dermatological Service and the Radiotherapy Department of The Mount Sinai Hospital.

nuclear leucocytes; 8 per cent lymphocytes and 2 per cent monocytes; Wassermann reaction 4 plus; sedimentation time, 70 minutes. Stool: guaiac test, 4 plus. Urine, essential



FIG. 1. Lesions on chest wall as they appeared in December, 1942



FIG. 2. Lesions on chest wall as they appeared in January, 1943

gative. Mantoux test, negative. A sternal marrow aspiration revealed normal activity and normal cell distribution. Cerebrospinal fluid, negative. A roentgen-ray examination of the chest showed a very large mediastinal mass extending both to the right and left; the lungs were not abnormal. Histological examination of the left supraclavicular node showed the characteristic changes of Hodgkin's disease.

Course. Radiotherapy was instituted and the patient was subsequently transferred to the Out-Patient Department for continuation of this therapy. While under treatment there it was noted that the lesions in the chest gradually showed a decreasing response to roentgen-ray therapy and the patient complained of increasing weakness.

The patient has also been under treatment for syphilis but had been very irregular in his attendance.

In January, 1942, a group of pea to quarter dollar sized, firm, tender nodules appeared on the chest over the manubrium sternum (figs. 1 and 2). These lesions gradually became con-

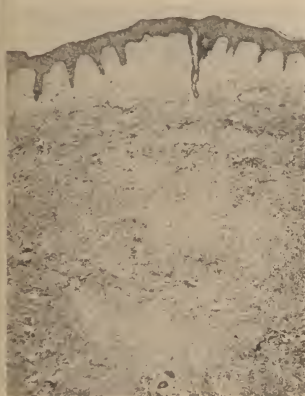


FIG. 3

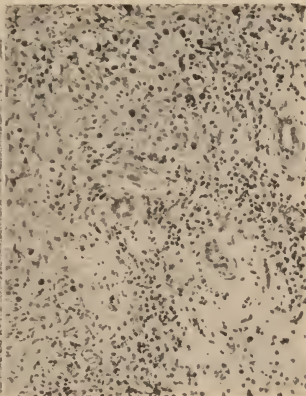


FIG. 4

FIG. 3. Section of skin taken from one of keloidal nodules on anterior chest wall

FIG. 4. High power magnification of center of section taken from skin showing pathognomonic features of Hodgkin's disease.

fluent and the central portion superficially ulcerated. A biopsy examination was performed at this time and reported as Hodgkin's disease of the skin. The histologic examination showed nodular, granulomatous lesions in the corium and subcutaneous tissue, particularly between the sweat glands. The lesions consisted of actively proliferating fibroblasts with large numbers of eosinophiles, numerous giant cells of the Sternberg type, plasma cells and lymphocytes. Necrotic foci were present in the center of the granulomatous areas. There was conspicuous intimal proliferation of the blood vessels (figs. 3 and 4). The lesions responded at first to radiotherapy but gradually became resistant. At the same time, numerous new nodules of a keloidal character developed around the original cutaneous lesions over the sternum as well as in the clavicular and axillary regions.

COMMENT AND SUMMARY

Lymphoblastomas are frequently accompanied by cutaneous manifestations. These may be localized or generalized, mild or intense in reaction and result in

non-specific and specific eruptions. Of the non-specific eruptions the most common complaint is a severe generalized pruritus frequently complicated by thickening and pigmentation probably induced by scratching. The non-specific eruptions may simulate urticaria, prurigo, eczema, neurodermatitis, psoriasis and parapsoriasis. They may be indistinguishable from herpes zoster, erythema multiforme, pemphigoid eruption, purpura, erythroderma, chloasma, alopecia and nail dystrophies from other causes. The roentgen-ray plays a most important role in the treatment of systemic and cutaneous Hodgkin's disease. Many patients may be kept in relatively good condition for a prolonged period of time. In the case reported here, palliation followed x-ray therapy, both in the system as well as in the cutaneous manifestations. However, the cutaneous lesions became radio-resistant and formed firm keloidal masses. The untoward response may have been predisposed by insufficient treatment for syphilis as well as by the known tendency to keloid development inherent in the skin of the Negro.

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IMMUNOLOGICAL APPROACH TO STUDIES ON CERTAIN DISEASES OF THE EYE¹

GREGORY SHWARTZMAN, M.D.

INTRODUCTION

Immunology is assumed to be primarily a science concerned with defensive processes of living organisms against disease-producing agents. The more recent advances, however, have brought out the fact that certain reactions of the organism to foreign agents have no protective value. On the contrary, it is with their participation that some substances by themselves completely harmless may become noxious when introduced into the body. For these reasons, immunology in a broad definition is a science of protection and hypersensitiveness. It is the purpose of my presentation to bring before you a review of phenomena of hypersensitiveness with special reference to the criteria employed for differentiation among various forms, and point out the possible etiological significance in some diseases of the eye. I shall also attempt to draw your attention to other possible approaches which were not fully utilized as yet for the study of certain ophthalmological problems.

ANAPHYLAXIS

There seem to exist different mechanisms capable of eliciting the state of hypersensitiveness of living cells and organized living systems to foreign agents. A large group of immunological events may be included under the heading of anaphylaxis due to the fact that essentially the same mechanism serves for production of injury. Antigens which are substances of a great variety stimulate production of antibodies when introduced parenterally. The interaction of antigens with the antibodies leads to formation of injury-producing factors which are held responsible for anaphylactic manifestations.

It is a matter of convenience to consider first the sub-group of anaphylactic reactions or so-called "true anaphylaxis" in which the antigens are of a large molecular weight, coagulable and soluble proteins, mainly of animal origin. It is also of advantage to separate the anaphylaxis of lower animals from anaphylaxis of man.

ANAPHYLAXIS OF LOWER ANIMALS

There exists a number of experimental observations which serve to prove the contention that antigens innocuous by themselves become markedly injurious

¹ From the Laboratories of Bacteriology of The Mount Sinai Hospital, New York City.

This paper embodies a lecture delivered before the Department of Ophthalmology, The Mount Sinai Hospital, on March 2, 1944 at the invitation of Dr. K. Lambert, Chief of Service. Since the presentation was intended to serve as a review of a vast immunological field in its application to ophthalmology, adequate credit could not be given to the numerous contributors who made the observations recorded. For further information the reader is referred to leading texts in immunology with special reference to Urbach's "Allergy"; papers by Wood and Burky, the author's monograph on "The Phenomenon of Local Tissue Reactivity" and Biological Abstracts for the past 5 years.

upon interaction with the specific antibodies. Thus a state of passive sensitization may be produced by the injection of specific antibodies into a normal animal. The subsequent injection of the innocuous antigen into the recipient animal gives typical symptoms of anaphylactic shock.

The remarkable feature is that widely different antigens interacting with specific antibodies produce the same symptom-complex resulting mainly from the involvement of smooth muscle. Obviously, different animal species show various manifestations of anaphylaxis depending on anatomical distribution of the shock tissues. Thus, carnivorous animals possessing a strong muscular coat of hepatic veins develop liver damage; guinea-pigs having well-developed bronchial musculature suffer from lung emphysema caused by bronchial constriction; while in rabbits the symptoms are found chiefly in the intestines, this being permitted by predominance of strong smooth muscles in the jejunum. Equally marked is shock to the muscular coat of arteries of all animals with resulting arterial constriction. The latter event leads to a long series of physiological changes, i.e. fall of blood pressure, edema, capillary dilatation, etc.

The mechanism of formation of the toxic factors as a result of the interaction is not quite clear. Dale's experiment seems to prove beyond question that the interaction occurs on the surface or within the tissue cells of the sensitized animal. Thus a strip of excised uterus from a guinea-pig sensitized prior to excision by a single antigen injection and washed free of body fluids may react with a strong contraction to the introduction of the antigen into the water-bath. In view of the fact that the response of the excised smooth muscle resembles the response to histamine, the theory was formulated that the toxic factor liberated by the antigen-antibody complex brings about production of a histamine-like substance. The hypothesis went through many phases of favor and disfavor. The recent investigations which seem to bring additional support to the theory are of interest but cannot be included here.

The local form of anaphylaxis in the rabbit (i.e. the Arthus phenomenon) is of special interest in connection with some ophthalmological problems. It is usually produced by repeated weekly subcutaneous injections of animal protein. Other sites, namely the eye may be used for its elicitation. After 6-8 weeks of treatment the tissues respond with marked local inflammation to the introduction of previously innocuous antigen. The histology of the lesion is characterized at its maximum by pronounced infiltration with polymorphonuclear leucocytes, swelling of epithelial cells, and edema of surrounding tissues which compresses the blood vessels. Diapedesis of red blood cells and central necrosis develop gradually and in relation to intensity of the inflammatory process. Thus the lesion may be considered as exudative and strongly inflammatory in nature, with hemorrhage and cell necrobiosis only as a supervening event. The sensitization is specific. Similarly to anaphylaxis, passive transfer of sensitization is made possible by the injection of serum containing antibodies (Opie).

ANAPHYLAXIS OF MAN

Although based essentially on the same mechanism, anaphylaxis of man shows certain differences from anaphylaxis of lower animals due to several reasons,

ely: the susceptibility of man to sensitization with some antigens is conditioned by certain constitutional and genetic factors; in anaphylactic sensitization occurring spontaneously the route by means of which the antigen establishes contact with the organism may influence the clinical manifestations; the antigens responsible for natural allergy are as a rule of considerably lower antigenicity than animal proteins used for elicitation of experimental anaphylaxis of lower animals. With the above general description of points of dissimilarity we may now define the essential forms of human allergy, as follows:

Serum sickness may be placed among the outstanding examples of human anaphylaxis.

One feature clearly differentiates this syndrome from anaphylaxis of lower animals to the same antigen. A single injection of serum is sufficient to elicit the syndrome. The symptoms develop, however, only after a certain incubation period during which antibodies develop against the serum. When the antibodies reach the necessary concentration they interact with the antigen remaining in the body, with the resulting production of an injurious antigen-antibody complex. The individual proteins of the serum differ antigenically requiring various intervals of time for the production of antibodies. This fact is responsible for repeated bouts of serum sickness following a single injection of serum. The assumption is supported by the main fact that injection of a purified single serum-protein never elicits more than one bout. According to Davidsohn, the individual proteins not only are responsible for differences in the length of the incubation period but also for the type of skin manifestations. Thus, it appears that euglobulin requiring an incubation period of 9 days is responsible for the urticarial eruption; the pseudoglobulin gives after a 12-day period of incubation a morbilliform rash, while the albumin elicits after 19 days of incubation the annular exanthema.

In view of marked fluctuation in individual susceptibility to the disease a greatly debated question still remains open, namely, whether the ability to develop the disease is contingent upon an innate factor. Those opposed to the theory of constitutional predisposition assume that the state of sensitization is produced prenatally by placental passive transfer of antibodies from the mother, and after birth by the natural oral and nasal introduction of the allied proteins found in animal meat, dandruff, and other skin sheddings of the respective animals.

It is of practical importance to differentiate the syndrome of serum sickness from the anaphylactic shock fortunately encountered only in a small percentage of patients injected with serum.

The symptoms observed in shock may be conveniently grouped according to their localization, namely: the skin, gastro-intestinal tract, and vascular, respiratory and nervous systems. The shock usually appears from several seconds to 30 minutes after the injection, although it may be sometimes delayed in appearance for several days. The symptoms are briefly, as follows: Quickly spreading urticaria; angioneurotic edema; vomiting; prostration; sweating; cough; and dyspnea with possible fatal termination.

It should be also noted that the manifestations of shock are frequently confused

with symptoms caused by primary toxicity of some therapeutic serum preparations, having no relation to anaphylaxis. They appear usually 45 to 90 min after an intravenous injection of the serum although less frequently may occur earlier or later. The symptoms are predominantly characterized by shock and thermal reactions, i.e. elevated temperature, chill, malaise and delirium.

Among the three types of response just described, it is only the serum sickness syndrome that presents some interest in reference to ocular reactions to parenteral introduction of foreign animal proteins and serves for their characterization.

There seems to be a tendency among clinicians to accept anaphylaxis as basis for some diseases in the absence of valid proof as to general, systemic anaphylactic sensitization. A supposition that an exclusively local anaphylactic sensitization of the eye may exist is contradicted by the clinical and experimental evidence available. The local anaphylaxis, or the Arthus phenomenon, in man is of exceedingly rare occurrence. Experimentally, when the animal is successfully sensitized, even in the local Arthus phenomenon, all the shock tissues become susceptible to anaphylactic injury. On the other hand, in general anaphylaxis the animal anterior chamber of the eye apparently participates with other organs in localization of antibodies and antigens from the circulation. Thus, Seeger and Seegal have shown that the specific antigen reappears in the sensitized anterior chamber of the rabbit upon the intravenous injection of the antigen. In this manner recurrent anaphylactic injury may be assumed to occur in sensitized eye.

It may be stated, on the basis of the facts just mentioned, that the existence of local anaphylaxis of the eye without general sensitization is quite improbable. The claims for an anaphylactic mechanism of an ocular reaction must be founded on the evidence of a systemic anaphylactic state, such as positive skin tests, positive passive transfer of sensitization and possibly desensitization. Additional supporting evidence may be offered by finding of specific precipitins for the antigen, or even by detecting the antigen itself in the circulation. With the use of a sensitive method of precipitation, the detection of the antigen in the aqueous humor may be attempted.

Also from the clinical evidence available on the relation between ocular and systemic anaphylaxis it may be concluded that ocular anaphylaxis to animal proteins may be taken to be a part of systemic anaphylaxis. However, it does not follow that systemic anaphylaxis must be necessarily accompanied by ocular anaphylaxis. This statement is made certain by information on the comparative incidence of positive ophthalmic skin tests in serum sensitive individuals. It appears that positive ophthalmic reactions appear in highly sensitive individuals while only in very rare cases anaphylactic shock is observed in the absence of an ocular reaction. Incidentally, it may be of interest to emphasize the value of the ophthalmic test for detection of serum sensitization, as a part of a following scheme recommended by Urbach: (1) the skin patch test is made in order to detect extreme sensitivity; when the test is negative: (2) the ophthalmic test is performed. When the latter is negative: (3) the antigen is injected intracutaneously.

In this combination of tests even the rarely occurring positive skin reactions accompanying the negative ophthalmic tests may be also discovered.

Under the anaphylactic group thus far presented the ophthalmic conditions characterized by acute manifestations of edema and inflammation of exudative type, mainly concerning the eye lids and the conjunctiva may be included. Since in these cases, the anaphylactic symptoms are usually due to the injection of animal serum the relationship between the inflammation and the anaphylactic mechanism is quite obvious. Nevertheless, etiological significance of this type of anaphylaxis in the following ocular syndromes present a greater interest, namely: the endophthalmitis caused by destruction of lens protein and uveitis; and sympathetic ophthalmia associated with liberation of uveal pigment. These diseases call for the examination of immunological evidence substantiating the possibility of auto-sensitization to homologous proteins released into the general circulation by a preceding trauma or operative procedure. According to the experimental work, certain homologous antigens may easily induce sensitization. These examples are found in paroxysmal hemoglobinuria in which autohemolysins are responsible for the destruction of homologous red blood cells.

Furthermore, certain cells and organs contain organ specific and species non-specific antigens which upon liberation into the general circulation may induce production of antibodies. The outstanding and proven examples of such antigens are the spermatozoa, lens protein, Rh agglutinogens of erythrocytes and uveal pigments.

The claim that endophthalmitis phaco-anaphylactica is caused by anaphylactic sensitization to homologous lens protein is fairly well supported by indirect evidence. The facts in favor of the assumption are as follows:

- (1) Lens protein is capable of producing antibodies in the homologous animal, though this is accomplished with difficulty and only after prolonged immunization.

- (2) The skin of patients suffering from the condition shows positive skin reaction to lens protein.

- (3) Desensitization of patients with the lens protein is said to be beneficial.

On the other hand:

- (1) Normal individuals may also react strongly to intradermal tests with lens protein.

- (2) Experimentally, animals sensitized to lens protein fail to develop endophthalmitis following injury to the lens. Burky assumed that staphylococcus products may enter into chemical combination with lens proteins, the resulting complex producing a potent antigen. In animals sensitized with the complex, eye-injury produced a violent endophthalmitis. This interesting hypothesis awaits further confirmation.

The assumption that sensitization to uveal pigments may also be responsible for some pathological conditions finds doubtful support. The evidence in favor of the hypothesis that in some cases of traumatic cyclitis the process of sensitization may cause low grade recurrent uveitis, is based on the finding of positive skin reactions to the pigment; and also in the fact that the uveal pigment is capable of producing antibodies in the homologous animal. Wood finds that in such cases the pigment produces foci of epithelioid cells and proliferation of pigmentary epithelium, i.e. and allergic proliferative type of response, while in

the absence of allergic sensitization there is seen only a non-specific histologic reaction to the pigment.

It suffices to mention that the theory of allergic nature of sympathetic ophthalmia finds little immunological support, inasmuch as no reaction of this type has ever been seen in any form of anaphylaxis.

ATOPY AND DRUG IDIOSYNCRASIES

Remaining forms of human anaphylaxis are the so-called atopy and drug idiosyncrasies.

In atopy the basic principle is again the formation of toxic agents through interaction of antigens with specific antibodies. The condition is, however, differentiated from other forms of anaphylaxis, first by the fact that the antigen is introduced into the body by natural contact; secondly, by the usual occurrence of sensitization to multiple antigens; and thirdly, by the fact that the antigens are of most varied nature. In most cases foods and pollens serving as antigens are of lower antigenicity than animal proteins. Here again, the outstanding feature of interest is that the symptom-complex bears no relation to the particular type of sensitizing substance. The symptoms may vary, however, with the particular route through which the reacting substance gains access to the shock tissue. It is in this manner, depending on the route of contact, that the eye may or may not participate in systemic atopy or may become the site of intense response. The remaining features, i.e. passive sensitization of Prausnitz-Küstner and desensitization are similar to other forms of anaphylaxis.

In references to eye diseases, the basic points differentiating atopy from induced protein anaphylaxis suggest a priori that several forms of ocular atopy may be encountered. The repeated sensitization over a prolonged period of time (for the duration of the pollen season, for example) and in small doses is likely to give rise to a chronic or recurrent inflammatory reaction, accompanied by tissue repair and formation of connective tissue. When the antigen reaches the sensitized eye tissues by way of the circulation there may be expected widespread involvement, i.e. conjunctivitis, uveitis and keratitis. In air-borne repeated sensitization the eyes may become the site of a more pronounced sensitization and, therefore, the site of more marked reaction than other parts of the body. The latter fact was experimentally shown to be the case in Ratner's experiments on guinea-pigs sensitized repeatedly by air-borne pollen dust. When supported by the findings of symptoms of systemic atopy, the theoretical suggestions may be advantageously borne in mind in considering whether a particular ocular condition is caused by atopic sensitization.

I shall not comment on acute ocular atopy which is obviously a local manifestation of a marked atopic systemic syndrome, as hay fever.

The etiology of vernal catarrh is of interest from the immunological point of view. There is clear and satisfactory evidence that atopic sensitization plays an important role in the causation of the disease, i.e., (1) seasonal occurrence, possibly with some exceptions; (2) frequent association of the condition with other systemic allergic symptoms; (3) possible elicitation of reaction in the cornea

junctiva with the aid of specific antigens; (4) improvement of the symptoms with administration of epinephrine; (5) the absence of bacteria and inclusion bodies; and finally (6) the presence of eosinophiles in conjunctival secretions. However, the marked enhancement of the lesion by exposure to light seems to be difficult to reconcile with the atopic etiology. Furthermore, in my opinion, the intense epithelial overgrowth appearing so strikingly in some forms of the disease suggests very strongly that some virus may at least in part participate in the etiology of the disease. I shall point out later the possible etiological relationships between viruses and antigen-antibody complexes.

Drug idiosyncrasies are apparently identical with the forms described above, in the mechanism of their production, i.e. all being contingent on antigen-antibody interaction. The idiosyncrasies occupy, however, an individual position due to two characteristic features:

The drugs being simple chemical substances and non-protein in nature are by themselves incapable of stimulating production of antibodies. According to Landsteiner and others, through a chemical process the drugs may combine with the native proteins of blood or tissues. The newly formed protein-drug compounds serve then as specific antigens capable of stimulating the production of antibodies. The interaction of the new antigens with the antibodies may in turn lead to the production of injury-producing factors. It is noteworthy that in this example as well, the symptoms obtained are not related to the pharmacological properties of the drug serving for sensitization.

Clinically well known ocular drug idiosyncrasies, as exemplified by atropin hypersensitiveness present no special interest from the general immunological point of view and, therefore, are left without further discussion.

BACTERIAL ALLERGY

The next group of hypersensitiveness about to be described is bacterial allergy. In this form no differentiation is necessary between human and animal forms in view of their identity. Bacterial allergy similarly to anaphylactic phenomena depends on the interaction of antigens with specific antibodies. There exist, however, prominent differentiating features which must receive our attention in view of the important role which bacterial sensitization apparently plays in ocular conditions.

The essential prerequisite for production of bacterial allergy is the existence of a focus of infection with living microorganisms, the most convincing studies having been made on tuberculin hypersensitiveness. Sensitization with dead tubercle bacilli is difficult requiring repeated injections of massive doses. The important manifestations of tuberculin hypersensitiveness could be conveniently considered as local, general and focal. All the effects are readily attributable to the same toxic agent resulting from the interaction of tuberculin with specific antibodies acquired by the animal in the course of the infection.

In the Koch phenomenon, live tubercle bacilli are injected instead of tuberculin, into the skin of an animal previously infected by an intradermal injection of the bacilli. In this experiment the opportunity arises to observe not only the

response of the sensitized skin to the tuberculin produced *in situ* by the bacilli of the second inoculation, but also to determine the ability of the skin to defend itself against the secondary infection. The evolution of the secondary tubercle is indeed quite different in all its phases from a primary infection. The histological response is non-specific and the lesion rapidly progresses to a large slough. This is promptly followed by a stage of complete healing of the lesion, while the primary tubercle remains ulcerated until the death of the animal. It is obvious that the initial phase of enhanced susceptibility is the manifestation of hypersensitiveness to products of tubercle bacilli; while the healing is due to immunity acquired following the primary infection.

The tuberculin hypersensitiveness was selected only as an example of experimental bacterial hypersensitiveness which may be elicited by a great variety of other microorganisms. Attempts to transfer this experimental information to interpretation of reactions of man to bacterial antigens are enormously complicated by many factors.

The first difficulties arise from the interpretations of skin tests to bacterial antigens, including tuberculin.

The tuberculin test occupies the most favorable position in this respect, although it is also beset by many limitations, which are well known to you.

The intensity of a reaction is by no means an indicator of the extent of the lesion, serving only to indicate the degree of the susceptibility of the individual; non-tuberculous infections may modify markedly the tuberculin response (i.e. exanthematous diseases, whooping cough); clinically inactive tuberculous foci may give positive reactions, while in the presence of extensive lesions the tests may be negative, etc. Thus, indeed, only a negative reaction repeatedly confirmed is of clinical value. It may be mentioned, that a "flare up" of a local lesion following injection of tuberculin confirms the specificity of a positive skin test.

When attempting to detect a state of hypersensitiveness to other bacteria additional handicaps are encountered. Some antigenic components may be commonly present in even unrelated bacteria. Positive skin reactions may be also caused by previous infections bearing no relation to the infection for diagnosis of which the skin test is being done.

I have mentioned these facts in passing merely in order to point out the diagnostic inadequacy of skin-testing with the majority of bacterial antigens, especially the streptococcus.

Tonight, however, our main concern is to evaluate to what extent the reactions of bacterial hypersensitiveness may constitute the underlying mechanism of production of certain ocular conditions.

The claims are so numerous that individual consideration of the disease syndromes is impossible. I would only like to bring to your attention the criteria which may serve usefully in the allergic interpretation of some lesions.

Broadly differentiated, in bacterial allergy the response of tissues to test antigens is delayed, while in atopy the reactions are immediate.

Histologically, three forms of focal and local reactions may be differentiated: (1) The progressive caseous type; (2) the exudative type; and (3) the prolifera-

tive type. Experimentally, bacteria-free antigens, and tuberculin alone may produce exudative and proliferative responses in the sensitized animal in the absence of live microorganisms in the local lesions. The sterile phlyctenular lesions and tuberculides of the exudative and especially proliferative types may be easily attributed to a state of bacterial hypersensitiveness. It would be erroneous, however, to insist that the lesions are tuberculous, the products of other bacteria being capable of eliciting similar lesions. The finding of the specific antigen responsible for sensitization presents an unsolved difficulty for reasons already given. The further handicap lies in the fact that the lesions mentioned may be also conspicuously modified by toxic factors of secondary bacterial invaders. The mechanism of this transformation and the experimental approach to the problem will be discussed at the end of the presentation.

Now to repeat, in all reactions described thus far, the toxic effects are elicited through the interaction of antibodies with antigens which by themselves are either innocuous or possess some doubtful toxicity.

TOXIN HYPERSUSCEPTIBILITY

In addition there exists also a group of antigens, the so-called true toxins which are defined by the following two characteristic properties, i.e. they possess primary toxicity eliciting specific lesions in the susceptible animal; and they stimulate after repeated injections the production of well-known antitoxins capable of abolishing the primary toxic effects.

Nevertheless, under certain experimental conditions, peculiarly at a time when the blood of an immunized animal shows a high antitoxic titer, an injection of small amount of toxin may give rise to a severe intoxication after a short incubation period with symptoms specific for the toxin used. Frequently the dose of toxin used may be too small to produce intoxication in normal control animals. The fact that the symptomatology is specific for the toxin used aids to differentiate toxin-hypersensitiveness from all the preceding forms of hypersensitiveness where the symptom-complex is the same with different antigens.

In the following reference to eye diseases I shall take up only those ocular toxic effects which are produced by the true toxins as defined immunologically. There are many clinical and pathological descriptions of lesions attributed to ill-defined toxic effects. Since the causative agents are of unknown nature, they must be left without comment. The true toxins produce only infrequently ocular lesions by direct extension from the bacterial foci. This is probably due to the fact that the toxins possess little spreading and penetrating power for the ocular tissues.

Among the examples of true toxic effects, the hemorrhagic lesions associated with pneumococcus infections are of interest. Experimentally, Parker was able to obtain from pneumococcus cultures toxins which provoke purpuric eruptions extending along the entire mouse tail following a subcutaneous injection into the tip.

According to Ayo, toxins which are responsible for the phenomenon of local tissue reactivity, to be described later, also possess an interesting primary toxicity

for the uveal tract. Upon the intravenous injection of the toxins there occurs a marked increase in permeability of the uveal blood vessels with appreciable increase in the protein contents of the aqueous humor. Upon withdrawal there occurs coagulation of the fluid. The speed of coagulation corresponds quantitatively to the amount of toxin injected.

Wood and Burky assume that a certain chronic and recurrent conjunctivitis may be caused by hypersusceptibility to staphylococcus toxins. As previously mentioned there exists experimental evidence that a state of toxic hypersensitiveness may be induced after repeated injections of toxin. The claim by Wood and Burky is also supported by a long series of investigations which clearly establish the existence of necrotizing staphylococcus toxin produced by certain pathogenic strains. This toxin apparently can be successfully neutralized by a specific antitoxin. According to the plan developed by the investigators, the treatment requires the isolation of a pathogenic type of staphylococcus. Ordinarily, an intradermal injection of a toxin diluted 1:100 into a normal individual gives rise to a moderate erythema. In hypersensitive individuals a dilution of 1:1000 may produce a similar reaction. A strongly positive reaction is indicated by necrosis at the site of the injection. Immunization of the patient is continued until the skin tests become negative.

While the staphylococcus ocular infection may be taken as an example of toxin hypersensitiveness, claims of a similar hypersensitiveness to toxins or to antigenic materials from other bacteria do not stand criticism. The skin reactions obtained are not clear-cut. As mentioned before, antigens may possess components commonly present in different bacterial species and, therefore, even strongly positive skin reactions cannot be regarded necessarily specific.

As may be remembered, it was stated at the beginning of the presentation that there may exist different mechanisms capable of inducing a state of hypersensitiveness or altered reactivity of the host, the interaction of antigen-antibody being only one of the mechanisms.

PHENOMENON OF LOCAL TISSUE REACTIVITY TO BACTERIAL FILTRATES

The phenomenon of local tissue reactivity to bacterial filtrates displays another mechanism of production of injury, as follows:

I shall omit the description of the fundamental experiment of this phenomenon, which I believe is well known to you and shall proceed with the main features which serve to characterize it.

The adult tissues and organs of man and animals are normally greatly refractory to certain toxic substances produced by a number of bacteria. These bacteria produce, however, substances which present a special interest. When they are injected intracutaneously or into the parenchyma of an organ, 6-24 hours later there is produced a local state of vulnerability in the injected site. Extensive investigations by many authors and my own studies have shown that this local state can be clearly differentiated and is not caused by local inflammatory changes; by blockage of the reticulo-endothelial system; and by enhancement of local capillary permeability. The state of vulnerability is clearly not

due to an anaphylactic process of sensitization. This belief is supported by many observations which cannot be presented in detail tonight, i.e. lack of passive transfer; the absence of local antibodies; the possibility to obtain cross reactions between unrelated antigens; etc. In view of this, the state is best described as that of induced reactivity resulting from some as yet unknown disturbances in the cellular physiological processes which avoid detection by presently available experimental means.

The elicitation of the state of reactivity constitutes the preparatory phase of the phenomenon. Now, while this state exists a variety of toxic agents introduced by way of the circulation are capable of inflicting dramatic damage upon the vulnerable tissue. The histological manifestations of the injury are primarily those of prompt abundant hemorrhage. It should be emphasized that the essential prerequisite of the phenomenon lies in the fact that the provocative injection must be given by way of the blood stream, or in other words, the mechanism necessary for the elicitation of the phenomenon consists essentially of two phases:

The first phase is the preparatory elicitation of reactivity which is followed by the second stage when the toxic agents are brought into contact with the vulnerable tissue by way of the blood stream. It is quite important to differentiate clearly the factors necessary for the elicitation of the state of reactivity from the factors provoking the reaction. While the preparatory agents can be only obtained under special experimental conditions from a limited group of microorganisms, the provocative factors may be obtained not only from certain bacterial cultures but are also found in other materials. A fact which may help us in the interpretation of certain clinical and pathological events to be discussed in a moment, is that a mixture of an innocuous protein-antigen with a specific antibody when injected intravenously is capable of producing severe damage in vulnerable tissues. Remembering that on one hand, the state of vulnerability is only induced by certain bacterial products; and that on the other hand, the antigen-antibody complexes are agents responsible for anaphylactic damage, we may find in this form of the phenomenon an illustrative example indicating the existence of a relationship between infection and atopy, a concept capable of elucidating certain clinical problems.

A survey of studies suggests that certain ocular diseases may be caused not by single etiological agents but by means of the concerted effects of multiple agents. The phenomenon just described demonstrates the existence of certain mechanisms which may facilitate our understanding of the pathogenesis of some diseases. It may be advantageous to emphasize again and amplify somewhat the following relationships brought out by this experimental work:

The state of vulnerability characteristic of the phenomenon under discussion may be elicited by certain bacterial toxins, localized bacterial infections and certain localized virus infections.

The vulnerable tissues may respond to the provocative factors which are certain bacterial toxins, non-bacterial antigen-antibody complexes, and live bacteria carrying the toxins.

The provocative factors are only effective when they reach the vulnerable tissue by way of the general circulation. The resulting lesions are conspicuously hemorrhagic and severely necrotic. Healing is preceded by ulceration and is accompanied by proliferation of connective tissue.

I do not intend to formulate any hypothesis concerning the etiological significance of these experimental data in certain ocular diseases. I would only like to illustrate the possible approaches to some ophthalmological problems by giving a few examples.

Thus a state of vulnerability of ocular tissues may be induced by bacteria or a virus normally present on the surface of the eye or in the conjunctival sac in the course of some insignificant infection. In vernal conjunctivitis, a complex of the atopic antigen with the specific antibody of the allergic individual may in turn be capable of producing injury in the vulnerable site by way of the vascular system. Provocative factors of a similar nature may be formed by the complexes of lens proteins or the uveal pigment with respective antibodies.

Phlyctenules, tuberculides and syphilides caused either by the products or the microorganisms themselves may be expected from the experimental evidence available to possess the necessary state of vulnerability to the same and other microorganisms of hematogenous origin. In congenital syphilis the state of reactivity may be induced by exposure of the surface of the eye to massive doses of *treponema pallida in utero*. After birth the state of reactivity may be maintained by persistence of small numbers of *treponema*. If the state of reactivity is thus locally maintained by a latent lesion the subsequent keratitis may later be elicited by the *treponema*, tubercle bacilli or other bacteria supplied from a distant focus by way of the general circulation. In this connection observations of Witebsky are of interest. According to him, new born rabbits remain totally refractory to the phenomenon up to a certain age when there occurs a sudden change to susceptibility. This finding may explain the absence of keratitis in the new born.

It may be pointed out again that in the first preparatory phase of the phenomenon the state of reactivity is elicited by the local injection. This is probably due to the fact that the preparatory factors are most effective when they have the opportunity of remaining in a local depot for the duration of some hours. However, the preparatory factors can also be brought into the site from the vascular system when a local state of capillary permeability produced with the aid of some agents permits the entry of the blood-carried toxins into the site. Thus a rabbit's ear is immersed into hot water, while an intravenous injection of a toxin is made through the vein of another ear. This first injection is taken to be equivalent to the local preparatory injection. Twenty-four hours later a second intravenous injection of the provocative toxin is made, whereupon a typical reaction appears in the ear which was immersed in hot water during the first injection. The modification is cited to point out that the phenomenon may be operative also in conditions when the preparatory factors reach the eye not from an ocular focus, as suggested thus far, but from a distant septic focus. The mechanism may explain ocular involvements accompanying systemic infections.

The purpose of these speculative remarks is solely to point out that *a priori* certain new approaches may be worthy of further investigations. I sincerely hope, however, that you will not consider them as attempts to formulate now any hypotheses as to the etiology of certain ocular conditions since I realize fully that considerable amount of additional work is necessary before these contentions may become acceptable and useful.

In view of the essential participation of the blood stream in the provocative phase of the phenomenon, the uveal tract and newly formed blood vessels of the cornea form a favorable reactive site. On the basis of this consideration and his experimental work Sanders suggests that the phenomenon may be the etiological basis of Eales's disease. Fabiani and Gunther observed that the normal rabbit cornea was refractory to the phenomenon. They succeeded, however, in eliciting an intense reaction of the phenomenon by inducing vascularization of the cornea prior to the experiment. In reference to phlyctenular keratitis Elder makes the following pertinent statement that "the usual reparative role of vascularization of the corneal ulceration is reversed, a circumstance which may be due to the continued transport of the exciting allergin into the sensitized cornea by the blood stream."

LIFE'S LATER YEARS

STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[New York City]

PART 4¹

THE CONTRIBUTION OF GREEK THOUGHT

Let us then reaffirm the toast: 'Whatever is Greek must, in the end, prevail!' for Greek thought abides on the heights of freedom, on upward pathways which science once deserted, indeed, but at the risk of its very existence.

Sudhoff-Essays

In the year 1550 B.C., as the Papyrus Elbers was being written, nomad tribesmen from the North were engaged in the conquest of the Greek peninsula and the islands of the Aegean Sea. These rude folk learned from their predecessor their neighbors, and also from far away peoples; "slowly they built up the greatest civilization that the world had seen" (1). In the poems of Homer (c. 1,000 B.C. celebrating the battles for the domination of the shores of Asia Minor, we find the earliest records of the religion and customs of this remarkable people whose great contribution was to be the achievement of intellectual freedom. The Orient, exemplified by the Egyptians, Babylonians, Hittites, Assyrians and Hebrews had made great strides forward in the physical and mental development of mankind, but "suffered from a lack of freedom of the mind, a kind of intellectual bondage to religion and old ideas" (1).

In the last book of the Odyssey, line 258, Ulysses gives advice to his father Laertes which indicates a sound understanding of the care of the aged

*Warm baths, good food, soft sleep and generous wine,
These are the rights of age, and should be thine.*

(Pope's translation)

Mackenzie (2) records Galen's opinion of this passage. "The poet's rule was excellent, which directed an old man after bathing and refreshing himself with food, to take some rest; for old age being naturally cold and dry, those things which moisten and warm, as bathing, eating and sleeping, are the most proper for it."

The great distinction achieved by Greek medicine may be traced to two primary sources, first, to the temples of Aesculapius, where the priests acted as physicians and through a mixture of faith and practical methods brought healing to the sick; and second, to the philosophical schools of Athens and its

¹ This is the fourth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting one of the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

and outposts. There taught men learned in the wisdom of Egypt and the East, such as Thales of Miletus (639-544 B.C.), Empedocles of Grigentum (444-404 B.C.) and Pythagoras (580-549 B.C.). These thinkers put aside the idea that the gods controlled the world, and attempted to explain the phenomena of life by ingenious hypotheses based in part on observation. From both sources came the knowledge of Hippocrates, the foremost physician of the age of Pericles, when philosophy was represented by Socrates and Plato, dramatic literature by Sophocles and Euripides, poetry by Pindar, satire by Aristophanes, art by Phidias and Polygnotus. A product of the temple school of Cos, a thinker in the best philosophic manner, the founder of modern medicine, he divorced medical thinking from both philosophy and religion, formulated its ethical code, and demonstrated for all time the value of sound observation and clear-headed reasoning. Among his many and varied contributions to the art of medicine is his emphasis on the patient himself, his habits, his food and his environment. In differentiating the peculiarities of man according to age, Hippocrates has recorded many sharp observations about the advanced years.

"And if at the rising of the Dogstar rain and wintry storms supervene and if the etesian winds blow, there is reason to hope that these diseases (dysentery) will cease, and that the autumn will be healthy; but if not, it is likely to be a fatal season of children and women, but least of all to old men."

Airs, Waters and Places, par. 10. (3)

"Of persons having empyema after peripneumonic affections, those that are advanced in life run the greatest risk of dying; but in the other kinds of empyema younger persons die."

On the Prognostics, par. 18.

"Acute pain of the ear, with continual and strong fever, is to be dreaded. Younger persons die of this disease on the seventh day, or still earlier, but old persons much later; for the fevers and delirium less frequently supervene upon them, and on that account. The ears previously come to a suppuration, but at these periods of life, relapses of the disease coming on generally prove fatal."

On the Prognostics, par. 22.

"Old persons are subject to cancers, both deepseated and superficial, which never leave them. They are particularly intractable when seated in the armpits, the loins and the thighs."

Ibid, p. 227.

"With regard to persons affected by the gout, those who are aged, have tophi in their joints, who have led a hard life, and whose bowels are constipated, are beyond the power of medicine to cure. But, the best natural remedy for them is an attack of dysentery, or other determination to the bowels. Persons, under opposite conditions, may be cured by a skillful physician."

Ibid, p. 217.

"With regard to the time when this (recovery from paralysis) may occur, it is to be prognosticated by attending to the severity of the disease, to its duration, to the age of the patient, and to the season, it being known that of all cases the inveterate, and such as are the consequence of repeated attacks, are the worst and the most difficult to remove, and those in aged persons."

Ibid, p. 222.

"Ischiatic diseases are to be thus judged of:—In the case of old persons, when the torpor and coldness of the loins and legs are very strong, and when they lose the power of erections, and the bowels are not moved, or with difficulty, and the feces passed with much mucus, the disease will be very protracted, and it should be announced beforehand that the disease will not last shorter than one year from its commencement."

Ibid, p. 223.

"When a person suddenly loses his speech, in connection with obstruction of the veins,—if this happens without warning or any other strong cause, one ought to open the internal vein of the right arm, and abstract blood more or less according the habit or age of the patient. Such cases are mostly attended with the following symptoms: redness of the face, eyes fixed, hands distended, grinding of the teeth, palpitations, jaws fixed, coldness of the extremities, retention of airs in the veins."

Appendix to the Regimen in Acute Diseases, par. 4.

"... In elder persons, and those in whom the heat is already more subdued, these cases (fever associated with headache, delirium and ocular symptoms) end in paralysis, mania and loss of sight."

The Epidemics, Book One, par. 6.

"In many cases erysipelas, from some obvious cause, such as an accident, and sometimes from even a very small wound, broke out all over the body, especially, in persons about sixty years of age, about the head, if such an accident was neglected in the slightest degree."

The Epidemics, Book Three, par. 4.

"Growing bodies have the most innate heat, they therefore require the most food, for otherwise their bodies are wasted. In old persons, the heat is feeble, and therefore they require little fuel, as it were to the flame, for it would be extinguished by much. On this account, also, fevers in old persons, are not equally acute, because their bodies are cold."

Aphorisms, Section One, No. 14.

"Largeness of person in youth is noble and not unbecoming; but in old age it is inconvenient, and worse than a smaller structure."

Aphorisms, Section Two, No. 54.

"Diseases about the kidney and bladder are cured with difficulty in old men."

Aphorisms, Section Six, No. 6.

"Persons are most subject to apoplexy between the ages of forty and sixty."

Aphorisms, Section Six, No. 57.

"People over forty years who are affected with frenzy do not readily recover; the danger is less when the disease is cognate to constitution and age."

Aphorisms, Section Seven, No. 82.

These quotations need no explanation and but little comment. They illustrate the amazing ability of Hippocrates both in observation and description. He realized the changing picture of disease with advancing age and continually gives home its special importance in prognosis. It is impossible here to quote all the relevant material, but the reader is strongly urged to turn again to the works of the master, where he will find familiar clinical pictures depicted vividly by one whose only instruments of precision were his five senses.

Edelstein (4) in a recent study of the relation of Greek medicine to religion and magic, points out it was essentially rational and empirical, but nevertheless influenced by religious ideas. God and his actions are powers reckoned with by physicians in their theory and practice. They refused to treat certain serious diseases where the result was foreordained, not from heartlessness, but on the assumption that the patient will seek treatment at the temple. The temple-cures boast of the god's success where the physician failed. A frequently quoted opinion of antiquity was that when the art of the physician fails, everybody resorts to incantations and prayers. Plutarch says, "Those who are ill with chronic disease and do not succeed by the usual remedies and the customary diet turn to purifications and amulets and dreams." Although Greek physicians acknowledged the power of religion, they rejected every form of magic as wrong, and never wavered in denunciation of superstition. These observations are to be correlated with similar discussions of the relation of medicine and religion in the preceding sections devoted to Primitive Man, Egypt, and the Old Testament.

In acclaiming the discernment of the Greek physician for his recognition of age generally as a factor in disease and for his emphasis on old age as a special stage of life, we must not fail to look into the general cultural attitudes and viewpoints of that period. For this purpose we have in Richardson's work (5) a contribution of the greatest value and relevancy. In a rare combination of erudition, insight and understanding, she has drawn a broad, detailed picture of the role of the aged in Greek life, based on a painstaking study of all possible original sources. We learn of the emphasis placed upon the respect for one's parents, and the high value placed upon the wisdom of the old. Certain duties and responsibilities belonged to the aged as well. On the other hand, the peculiarities, foibles and eccentricities of the hoary-headed were not only recognized but formed a frequent source of humor and satire. The Greeks did not delude themselves about old age, for all references to it are highly realistic, and stress its unfavorable and unpleasant nature, at times regarding it as a punishment sent for that purpose by Zeus. Dr. Richardson's study of the artistic representations is no less comprehensive than the survey of the literary sources.

The excellent reproductions of the paintings on pottery and of sculptures indicate clearly that the Greek artist had a keen eye for the physical characteristics of the aged (fig. 1). The treatment of the old man as a clown in the Greek drama



FIG. 1. Old Woman on the Boston Counterpart of the Ludovisi Altar (Boston Museum of Fine Arts). Reproduced by permission from *Old Age Among the Ancient Greeks*, by Bessie Ellen Richardson, Baltimore, Johns Hopkins Press, 1933.

Dr. Richardson points out that "this is a remarkable picture of old age for the period (480-470 B.C.). . . . The profile of the old woman reveals a hooked nose; the lips suggest toothless gums; the cheeks are slightly sunken; the chin sags; and the bones of the shoulder almost show through the wasted flesh; the hair is bobbed and treated in rather severe straight waves. It is a picture of respectable old age, not the courtesan type, and the bobbed hair may be taken as a sign of mourning."

was imitated centuries later in the Italian *commedia dell'arte*, where he became the character Pantalone, a word used as a synonym for old man by Shakespeare.

The opinions of Plato and Aristotle on old age have served for over two thousand years as either model or inspiration for untold numbers of writers, many of whom, like Cicero, neglected to quote their authorities. In the open

g pages of the first book of the dialogue known as *The Republic*, Plato tells of Socrates' conversation with Cephalus, the aged father of Polemarchus, in which the philosopher urges the old man to tell him his opinion and experience of the advancing years.

"I will certainly tell you, Socrates, what my experience of it is. I and a few other people of my age are in the habit of frequently meeting together, true to the old proverb. On these occasions, most of us give way to lamentations, and regret the pleasures of youth, and call up the memory of amours and drinking parties and banquets and similar proceedings. They are grievously discontented at the loss of what they consider great privileges, and describe themselves as living well in those days, whereas now, by their own account, they cannot be said to live at all. Some also complain of the manner in which their relations insult their infirmities, and make this a ground for reproaching old age with the many miseries it occasions them. But, in my opinion, Socrates, these persons miss the true cause of their unhappiness. For if old age were the cause, the same discomforts would have been felt also by me, as an old man, and by every other person that has reached that period of life. But, as it is, I have before now met with several old men who expressed themselves quite in a different manner; and in particular I may mention Sophocles the poet, who was once asked in my presence, 'How do you feel about love, Sophocles? are you still capable of it?' to which he replied, 'Hush! if you please: to my great delight I have escaped from it, and feel as if I had escaped from a frantic and savage master.' I thought then, as I do now, that he spoke wisely. For unquestionably old age brings us profound repose and freedom from this and other passions. When the appetites have abated, and their force is diminished, the description of Sophocles is perfectly realized. It is like being delivered from a multitude of furious masters. But the complaints on this score, as well as the troubles with relatives, may all be referred to one cause, and that is, not the age, Socrates, but the character of the men. If they possess well-regulated minds and easy tempers, old age itself is no intolerable burden: if they are differently constituted, why in that case, Socrates, they find even youth is irksome to them as old age."

" . . . And to those, who, not being rich, are impatient under old age, it may be said with equal justice that while on the one hand, a good man cannot be altogether cheerful under old age and poverty combined, so on the other hand, no wealth can ever make a bad man at peace with himself."

" . . . But if his conscience reproaches him with no injustice, he enjoys the abiding presence of sweet hope, that 'kind nurse of old age,' as Pindar calls it. For indeed, Socrates, these are beautiful words of his, in which he says of the man who has lived a just and holy life, 'Sweet Hope' is his companion, cheering his heart, the nurse of age,—Hope, which more than aught else steers the capricious will of mortal men" (6).

This pleasant kindly attitude of the philosophers contrasts sharply with the views of Aristotle (384-322 B.C.), who, in Garrison's words, "gave to medicine the beginnings of botany, zoology, comparative anatomy, embryology, teratology and physiology, and the use of formal logic as an instrument of precision." Aristotle's theory of old age is that heat is lost by gradual dissipation, very little remaining in old age — a flickering flame that a slight disturbance could put out. The lung hardens by gradual evaporation of the fluid and so is unable to perform its office of heat regulation. He assumes that heat is gradually developed in the heart. The amount produced is always somewhat less than that which is given off and the deficiency has to be made good out of the stock which with the organism started originally, that is, from the innate heat in which the soul was incorporated. This eventually is so reduced by constant draughts made up for it that it is insufficient to support the soul. The natural span of life, he says, differs greatly in length in different species, due to material constitution as well as the degree of harmony with the environment. But still, as a general rule, big plants and animals live longer than small ones; sanguineous or vertebrate longer than the invertebrates; the more perfect longer than the less perfect; and long gestation generally goes with long duration. Thus bulk, degree of organization, period of gestation, are correlated. Great size goes with high organization.

In his *Rhetoric*, as is well known, Aristotle gives old age an unfavorable aspect. He says in substance that the old have lived many years and been often the victims of deception, and since vice is the rule rather than the exception in human affairs, they are never positive about anything. They "suppose" and add "perhaps" or "possibly," always expressing themselves in doubt and never positively. They are uncharitable and ever ready to put the worst construction upon anything. They are suspicious of evil, not trusting, because of their experience of human weakness. Hence they have no strong loves or hates but go according to the precept of bias. Their love is such as may one day become hate and their hatred such as may one day become love. The temper of mind is neither grand nor generous—not the former because they have been too much humiliated and have no desire to go according to anything but mere appearances and not the latter because property is a necessity of life and they have learned the difficulty of acquiring it and the facility with which it may be lost. They are cowards and perpetual alarmists, exactly contrary to the young; not fervent but cold. They are never so fond of life as on their last day. Again, it is the absent which is the object of all desire, and what they most lack they most want. They are selfish and inclined to expediency rather than honor; the former having to do with the individual and the latter being absolute. They are apt to be shameless rather than the contrary and are prone to disregard appearances. They are dependent for most things. They live in memory rather than by hope, for the remainder of their life is short while the past is long, and this explains their garrulity. Their fits of passion though violent are feeble. Their sensual desires have either died or become feeble but they are regulated chiefly by self-interest. Hence they are capable of self-control, because desires have abated

and self-interest is their leading passion. Calculation has a character that regulated their lives, for while calculation is directed to expediency, morality directed to virtue as its end. Their offenses are those of petty meanness rather than of insolence. They are compassionate like the young, but the latter are so from humanity while the old suppose all manner of sufferings at their door. When the orator addresses them he should bear these traits in mind. Elsewhere he says a happy old age is one that approaches gradually and without pain, and is dependent upon physical excellence and on fortune. though there is such a thing as a long life even without health and strength (7).

The great naturalist believed that gray hair resulted from weakness and deficiency of heat, and that baldness arose from overdeveloped sexual feeling. Grayness, he held, results from decay of the liquid nutrient of the hair, but does not necessarily indicate physical deterioration.

The important contributions of the Alexandrian School are well known but do not bear directly on our theme. As the power of Rome grew in the ancient world, the influence of the Greek physician broadened, and for our further investigations we shall turn to the Imperial City. Many centuries will pass before mankind learns to build on the broad strong foundations laid out by Greek scientists and philosophers.

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ESSAYS ON THE BIOLOGY OF DISEASE¹

ELI MOSCHCOWITZ, M.D.

CHAPTER 6

THE BIOLOGY OF POLYCYTHEMIA VERA

In the final analysis the essential diagnostic differential between uncomplicated true polycythemia vera and secondary polycythemia due to hypertension of the pulmonary circuit or to prolonged mountain sickness, is the normal oxygen saturation of the blood (1). Nevertheless, Harrop and Heath (2) found that in polycythemia vera during exercise there is a lowered diffusion of oxygen. However, Barach and McAlpin (3) treated two patients by confining them in an atmosphere of 50 per cent oxygen for 15 and 17 days respectively without avail. This makes it very unlikely that anoxemia is a factor in the production of polycythemia vera.

This explains the ruddy complexion of the patient with true polycythemia vera as opposed to the blue color of those afflicted with secondary polycythemia. It is generally believed that true polycythemia is distinguished from the secondary variety by the increase in the total blood volume. This distinction is not valid because I have observed on a number of occasions that if the blood volume is followed in patients with secondary polycythemia, it eventually increases often to degrees witnessed in true polycythemia. Apparently an increased blood volume is the final compensatory mechanism for the continued anoxia, comparable to the loss of concentrating ability and consequent polyuria observed in progressive renal insufficiency.

Being a disease of many years duration and of insidious onset, the opportunity to observe the entire life cycle of the malady is rare indeed. The earliest phase is practically unknown. Harrop (4) states that in the course of routine blood examinations in students, it is not unknown to find one or more students with a high erythrocyte count. In two instances studied by Harrop the spleen was definitely palpable. He quotes Lommel (5) who reports similar observations. Rosenthal and Bassen (6) also report asymptomatic cases that were discovered in the course of routine examination.

Under ordinary circumstances, the patient with true polycythemia pursues a life for years with a fair degree of efficiency and free from complications. Occasionally, hypertension arises, an association that Gaisbock (7) tried to create as a separate disease entity, but it is now generally held that this association is

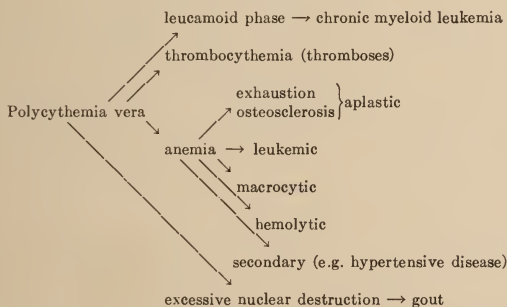
¹ This is the sixth chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt is made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed

mere coincidence, related to the age incidence. The only mechanism whereby true polycythemia may give rise to hypertension is the increased viscosity of blood but this would affect the blood pressure by a rise of but a few millimeters of mercury. Nevertheless, the cardiovascular-renal syndrome arising from essential hypertension is by no means an infrequent association. I have seen a number of such cases. In all phases of the disease, patients with polycythemia vera are subject to thromboses, both arterial and venous. [Oppenheimer (8), Brown and Griffen (9), Diedercke (10).] These are largely the result of the thrombocythemia, so commonly present in polycythemia vera (vide later). In part they may also be due to the high blood calcium which has been reported by some observers. (Brown and Griffen (97).)

Typical gout is by no means an infrequent complication of polycythemia vera. I have seen about three or four such cases. This complication has been reported by many observers, for instance by Reifstein (11) and Weber (12). The

Biology of Polycythemia Vera



gout is probably the result of the extensive nuclear destruction consequent upon the excessive production of erythrocytes. This also explains the occasional high uric acid content of the blood (Isaacs (13), Shelburne and Hanzel (14), Erickson (15).)

Transition of polycythemia vera to leukemia. As a rule, there is a leucocytosis as well as an erythrocytosis in polycythemia vera, which usually is progressive, so that white blood counts of even 20 to 30000 per cu. m.m. are by no means uncommon. Also in most instances of long duration, myelocytes and other forms of immature leucocytes appear in the blood, corresponding to an increase in the leukoblastic elements in the bone marrow. Minot and Buchman (16). This phase of the disease is often referred to as the *leukemoid*. Eventually a blood picture typical of that of true leukemia may ensue. (Minot and Buchman (16), Rosenthal and Bassen (6), Reifstein (11), Klump and Herzberg (17), Hedenius (18), Blumenthal (19), Prendergass and Pancoast (20), Herxheimer (21).) Furthermore, the blood picture does not merely represent an increased leukoblastic

activity of the bone marrow, but a true leukemia, this is shown by post-mort studies in which true myeloid leukemic infiltration is found. (Minot and Buchman (16), Rosenthal and Bassen (6), Klump and Herzberg (1), Hedenius (18), Reifstein (11). How frequent the transformation of polycythemia vera into leukemia occurs cannot be affirmed with any assurance because observations upon this disease are usually limited to only a small cross-section of its life cycle, but that it is fairly common is indicated by the observations of Minot and Buchman (16) who report this transition in three out of fifteen cases. The cause of this transformation is as obscure as the cause of polycythemia vera and of leukemia. Some have suggested that the malady bears many of the earmarks of a malignant neoplasm.

Transition of polycythemia vera to anemia. I have observed a number of untreated cases of polycythemia that eventually developed anemia. A considerable number of observers have reported such transitions. The anemia is of various types. Thus Minot and Buchman (16) report three cases all of which showed leukemic blood pictures, one showing the typical anatomical changes of leukemia at autopsy. This type of anemia accompanies most of the reported cases of transition from polycythemia vera to leukemia. A second type of anemia is the aplastic as reported by Rosenthal and Bassen (6), Freund (22) and Hirschfeld (23). In two of Rosenthal and Bassen's cases this type was accompanied by osteosclerosis of the bone marrow, similar to that observed by Hirschfeld (23). An anemia resembling hematologically macrocytic anemia has been reported by Delboughe, Gotschlick and Froboese (25) and others. Whether these are biologically transitions to true pernicious anemia is very much open to question. There are a few reports of transitions to an anemia of the hemolytic type indicated by an increased output of urobilin and an increased fragility of the erythrocytes. (Minot and Buchman (16), Weber (12), Mosse (26), Avery (27). When hypertensive disease is associated, a secondary anemia may result when the hypertensive disease reaches its terminal nephritic phase.

The anemias following treatment by radiation, benzol or phenylhydrazine, repeated venesection obviously are not relevant in a discussion of the biology of polycythemia vera.

It is obvious that the cause of the anemia that is occasionally observed as a terminal event in polycythemia is various. Overstimulation of the bone marrow, a view expressed by Harrop (2) is a plausible explanation but may be regarded as only one of the factors.

Transition of polycythemia vera to thrombocythemia. A priori, one would expect that the third morphological component of the blood, namely the blood platelets, would occasionally partake in the general rise accompanying the erythrocytic and leukoblastic activity in the bone marrow and this, indeed, is found to be the case. An increase in the megakaryocytes in the bone marrow has been reported by numerous observers. Minot and Buchman (16), Hutchison and Miller (28), Askanazy (29), Weber (12) and Di Guglielmo (30) and Rosenthal and Bassen (6). Indeed, Minot and Buchman (16) have occasionally discovered them in the peripheral blood. Accompanying this increase in megakaryocyte

here is a thrombocythemia. This transition must be common because Rosenthal and Bassen (6) in a wide experience found a thrombocythemia in 30 per cent of their cases. The relation between the thrombocythemia and thromboses has already been commented upon.

It is evident therefore, that polycythemia vera at any particular cross section of its clinical course does not necessarily imply that it is an end result. Its evolution is various, depending on incidental complications and the opportunity to observe the malady over a prolonged period. If one sees the disease in one of its terminal phases, for instance, the leukemic, it is sometimes difficult to reconstruct the previous clinical course. There are probably many cases of what appears to be a primary chronic myeloid leukemia that were originally cases of polycythemia vera.

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MASSIVE PULMONARY EMBOLISM. III¹

BASED IN PART ON A STUDY OF EIGHTY-EIGHT FATAL CASES²

HAROLD NEUHOF, M.D. AND SAMUEL H. KLEIN, MAJOR, MC., A.U.S.³

[New York City]

II. THE MECHANISM OF DEATH IN PULMONARY EMBOLISM

The pathologic physiology of pulmonary embolism is of great therapeutic as well as of theoretical interest, and has been the subject of considerable controversial discussion in the literature. The views of various authors have been derived partly from clinical and partly from experimental observations. Merlowitz (59) has reviewed these theories and has divided them into four categories. The clinical phenomena following pulmonary embolism have been attributed

1. Asphyxia (60, 61);
2. Acute right heart failure (60, 62, 63);
3. Reflex cardiac standstill (64, 65), reflex inhibition of the respiratory center (63), reflex vasomotor shock (66);
4. Obstruction of the flow of blood to the left heart with a consequent reduction in its output (60, 67, 68).

Concerning the causation of death Churchill (3) defines at least three mechanisms by which death is produced when a large thrombus is carried through to the right heart and lodges in the pulmonary artery: 1) Complete obstruction with immediate death; 2) partial obstruction with delayed death due to reduced effective blood volume; 3) partial obstruction with delayed death, in which right heart failure is a component. He states that the duration of life and the symptomatology will depend upon the amount of obstruction that the embolus produces in the particular case under consideration.

Pilcher (69) also feels that death is usually caused by obstruction of the pulmonary circulation. He records three types of death: 1) Sudden death (instantaneous to within 10 minutes); 2) rapid death (from 10 minutes to 1 hour) and 3) gradual death (more than 1 hour). In analysing those "good" lives in which death was due to embolism and to no other important contributing cause he found that in 37 out of 40 cases the embolism was obstructive. In his opinion when death follows a small embolism it can rarely be attributed to the embolism alone. He (79) explains the mechanism of slowly fatal embolism as being due to an incompletely obstructing embolus becoming complete as a result of accretion.

¹ This is the third installment of a series of articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting one of the Series of projected Monographs. The Mount Sinai Hospital Press.—Ed.

² From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital, New York.

³ Major Klein, adjunct surgeon to The Mount Sinai Hospital and now serving overseas with The Mount Sinai Hospital Unit, has contributed the study of the fatal cases and the analysis on which the work is based.

Gibbon and Churchill (70) also stress the importance of the mechanism of obstruction in the production of the clinical manifestations of pulmonary embolism. Correlating the clinical classification of Rochet (71) with their own experimental observations, they believe that the following assumptions are warranted: If pallor and lowered blood pressure predominate in a patient suffering with pulmonary embolism (the "syncopal" type of Rochet) the embolus reduces the greatest degree of obstruction in the pulmonary artery at or above the point of bifurcation. When cyanosis is a predominant feature and the lowering of the blood pressure is slight or absent, (the asphyxial type) the embolus blocks at least one main branch of the pulmonary artery and possibly some of the smaller branches of the other. Increased depth of respiration occurs in both clinical types.

Villaret and his co-workers (72), on the other hand, state that pulmonary arterial occlusion and insufficiency of the pulmonary circulation are too frequently cited as explaining the fatal outcome of a thrombus in the pulmonary artery. They state as evidence that clinically a large artery may be obstructed by a clot, yet death does not occur immediately, as shown by the fact that the operation initiated by Trendelenburg can be performed to remove the clot. On the other hand, sudden death may follow block by a relatively small clot and resultant interference of circulation of only a small pulmonary area. Further, during lobectomy or pneumonectomy, ligation of a single branch or all the branches of a pulmonary artery is unavoidable, yet no asphyxia results. The authors present two theoretical explanations for the action of a pulmonary embolism. Either the embolus directly affects the respiratory and circulatory functions of the lung, or the acute block starts up a series of general phenomena of a reflex character. On the basis of an extensive physiopathologic study (72), they have come to the conclusion that both explanations are correct, but, depending on the individual case, each includes only a portion of the real underlying factors. Experimentally emboli of various sizes were produced in dogs. It was found that large emboli did not cause death but that death occurred if many pulmonary arterioles were blocked. From these experiments it was concluded that sudden death is not due to an obstruction of the pulmonary circulation but to the result of a reflex through the action of the embolizing particles acting on the nerve terminations in the arterioles and not in the arteries or capillaries.

DeTakats and Jesser (2) also suggest that factors other than the mechanical plugging of the pulmonary circulation may operate to produce the manifestations of pulmonary embolism. They noted eight instances in a group of thirty autopsied patients who had died of pulmonary embolism, in which the main pulmonary artery was patent and only the left or right pulmonary artery or a small branch was obstructed. In another paper, evidence is presented by DeTakats, Beck and Fenn (84), that death from pulmonary embolism is not always due to asphyxia, failure of the right heart, or insufficient venous return to the left heart. These conditions prevail only when the main pulmonary artery or both right and left branches are simultaneously obstructed. However, post-mortem

records indicate that patients may die from a small embolus obstructing insignificant area of the lung. In addition, the authors have shown in the animal experiments that dogs when given a fatal quantity of embolizing material may be saved in at least fifty per cent of the cases if they receive atropine or their vagi are cut. Electrocardiograms of dogs have also been presented (DeTakats and Fenn (76)) which indicate strong vagal effects on the heart which may be abolished by atropine. On the basis of these animal experiments and others which deal with vagal effects on the bronchial tree and the gastrointestinal tract, these workers feel that a widespread radiation of autonomic reflexes occurs during pulmonary embolism which may contribute to the cause of death.

Villaret and his associates (72) have also shown, in dogs and rabbits, that in addition to neurovegetative factors, humoral factors are important modifiers of the reaction to embolism. It was found that once a dog has received ephedrine, atropine, and sodium bicarbonate, rapid death can no longer be produced with embolism identical with that which would previously have been lethal. On the contrary, acidosis obtained by intravenous injection of a solution of hydrochloric acid causes embolism to become much more rapidly fatal. Alkalosis produced by intravenous injection of a solution of sodium bicarbonate causes the embolism to become fatal more slowly. Although division of the vago-sympathetic trunk is without immediate effects in dogs, division of the vagi in rabbits necessitates an increase in the amount of powdered pumice stone required to produce death from embolism. On the other hand, a smaller fatal dose is needed in rabbits when both sympathetic trunks are divided.

Mendlowitz (59) has produced massive pulmonary embolism in dogs and evaluates the theories of the mechanism of the physiologic changes set up by pulmonary emboli. His data do not support the neurogenic theories. Since death was not instantaneous in his experimental animals but took place at least several minutes after embolism, Mendlowitz feels that it is unlikely that we are dealing with reflex cardiac standstill or reflex inhibition of the respiratory center. There is also no evidence of vasomotor collapse since, if anything, a reflex vasoconstriction must occur as a part of the compensatory mechanism tending to prevent the arterial blood pressure from falling. From these experiments there was no evidence bearing on the suggestion of Peiser (76) that reflex spasm of the pulmonary artery augments the obstruction caused by the embolus.

As regards the other three concepts namely, obstruction, asphyxia, and heart failure, Mendlowitz states that they are in reality facets of the entire complex associated with massive pulmonary embolism. The primary factor is, in the last analysis, the obstruction itself which, because of the increase in resistance it interposes, dissipates some of the energy of the right heart and thereby leads to a reduction in the output of this chamber and hence also that of the left heart. There is also no evidence from this work pointing to acute heart failure as a contributory cause early in the sequence of events. Heart failure may develop secondarily as a result of a deficient coronary blood flow aided in some instances by arterial anoxemia.

From the foregoing discussion, it seems that the primary factor in all the changes following massive pulmonary embolism is the obstruction itself which causes a reduction in minute volume flow and a redistribution of blood in the regulatory system. All the other phenomena are sequelae, and death is eventually due to anoxia of the heart, of the respiratory center, or of both

III. PATHOLOGY AND SYMPTOMATOLOGY

According to various observers as well as to an analysis of our own cases the symptomatology of pulmonary embolism is composed of widely varying clinical pictures of all grades of severity and duration, the component symptoms occurring in many clinical combinations depending upon the number, size, location and chronological sequence of the embolizations and the secondary pathologic-physiologic changes which they produce.

As stated by Belt (24), careful routine dissection of the lungs at autopsy reveals a much higher incidence of pulmonary embolism than is commonly recognized. We have reviewed a large series of protocols of post-mortem examinations performed at the Mount Sinai Hospital and have noted many instances in which small pulmonary emboli, infarctions and occasionally even massive embolism occurred which were unsuspected during life. Such cases escaped recognition for a variety of reasons: absence of characteristic clinical manifestations, similarity of the symptoms to those produced by other conditions, the nature and severity of an underlying illness which masked the symptoms of pulmonary embolism or diverted attention from them.

Pulmonary embolism may occur at any time during a medical illness or the surgical postoperative period. We have records of pulmonary embolism occurring as early as 15 to 20 minutes and as late as 10 weeks after operation. The time of occurrence of the fatal pulmonary embolism in the surgical cases in our series is charted in Tables 7 and 8. Twenty-one occurred in the first week, of which 14 took place on the third, fourth and fifth days. There were 26 fatal embolisms in the second week, mainly between the eighth and twelfth days. Thus, 47 cases of fatal pulmonary embolism in a group of 62 surgical patients occurred in the first two weeks after operation. Of the remaining 15 fatal embolisms, 6 took place in the third week, 3 in the fourth, 5 between the fifth and ninth weeks inclusive, and one ten weeks after operation.

Cleland (11) states that massive (fatal) pulmonary embolism may occur as soon as the second or third day after a severe abdominal operation, although the majority of cases center around a period of about ten days. Pilcher (10) in his extensive statistical survey, notes that the incidence of fatal pulmonary embolism postoperatively rises until the fifth day. The incidence is then fairly constant until the ninth day and then falls off. In a group of 537 postoperative cases 60 fatal pulmonary embolisms occurred in the first four days, "a period often regarded as safe." Petterson (93) has reported 3 cases in which pulmonary embolism occurred while the patient was on the operating table.

In their series of 897 cases of pulmonary embolism (fatal and non-fatal), Barker et al. (126) found that in approximately one-fourth the embolism oc-

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curred before the seventh postoperative day; in approximately one-half cases, from the seventh to the fourteenth day, inclusive; and in approximately one-fourth, after the fourteenth day. This was also true of the group in which fatal embolism occurred (343 cases). The earliest fatal embolism occurred the first postoperative day; the latest on the fifty-eighth.

Pulmonary embolism may occur as a single event or in the form of successive episodes. The first attack may cause death, or the fatal episode may occur after one or more embolisms. The initial embolisms may produce mild or symptoms, or, in some cases, a severe clinical picture.

TABLE 7
Occurrence of fatal pulmonary embolism during the postoperative period

<i>Day</i>	<i>Number of cases</i>
1st	2
2nd	2
3rd	3
4th	4
5th	7
6th	1
7th	2
	21 in the 1st week
8th	6
9th	2
10th	6
11th	5
12th	4
13th	1
14th	2
	26 in the 2nd week
15th	2
16th	0
17th	1
18th	2
19th	0
20th	1
21st	0
	6 in the 3rd week
22nd-30th	3 during the 4th week
31st-59th	5 " the 5th to 9th week
10th week	1 " the 10th week

In order to reconstruct and evaluate the course of events in our series of cases of fatal pulmonary embolism we have attempted to correlate the autopsy findings with the clinical picture. According to the records of this group of 80 cases, 43 presented features at necropsy indicating that one or more previous pulmonary embolizations had occurred hours, days or weeks prior to the one which caused death. The great majority of these 43 cases (36) presented clinical signs or symptoms relating to the earlier pulmonary embolic episodes. It is probable that there were warning earlier clinical manifestations in some of the remaining 45 cases which were not recorded.

TABLE 8

Analysis of the fatal cases of pulmonary embolism with reference to time of onset, possibility of diagnosis, and operability

SE- M- R	POSTOPERATIVE DAY OF THE FATAL PULMONARY EMBOLIZATION	INTERVAL BETWEEN FATAL EMBOLI- ZATION AND DEATH	CLINICAL DIAGNOSIS OF THE TERMINAL EPISODE	IN CASES IN WHICH NO DIAG- NOSIS NOTED ON HOSPI- TAL CHART, COULD IT HAVE BEEN MADE FROM THE CLINICAL PICTURE?	BASED ON THE POSTHOREM FINDINGS, WAS THE TREN- DELBURG OPERATION FEASIBLE?	ASIDE FROM THE PULMO- NARY EMBOLUS, WAS THE CASE HOPELESS?
1	8th day	3½ hours		Yes	No	Yes
2	8th day	25 minutes		Yes	Yes	No
3	11th day	15 to 20 min.	Pulmonary embo- lism? Coronary thrombosis?		Yes	No
4	14th day	10 minutes		Yes	No	No
5	36th day	8 hours	Myocardial failure		Yes	No
6	Non-operative	6½ days	Pulmonary embo- lism? Coronary thrombosis?		No	Yes
7	Non-operative	Progressively downhill course		No	Yes	Yes
8	14th day	24 hours	Pulmonary embo- lism? (insulin shock?)		Yes	No
9	Non-operative	15 minutes	Coronary throm- bosis		Yes	No
10	2nd day	7½ hours	Coronary throm- bosis		Yes	Yes
11	7th day 11th day	10 minutes	Pulmonary embo- lism? Pulmonary embo- lism? (Coronary thrombosis?)		?	No
12	4th and 10th days	2 days	Pulmonary in- farction		No	No
13	32nd day	22 minutes		Yes	Yes	No
14	20th day	4 days	Functional myo- cardial involve- ment		Yes	Yes
15	Non-operative	Several days		No	No	Yes
16	59th day	10 minutes		Yes	Yes	No
17	10th day	25 minutes		Yes	Yes	No
18	11th day	Few moments		Yes	Yes	No

TABLE 8—Continued

CASE NUM- BER	POSTOPERATIVE DAY OF THE FATAL PULMONARY EMBOLIZATION	INTERVAL BETWEEN FATAL EMBOLI- ZATION AND DEATH	CLINICAL DIAGNOSIS OF THE TERMINAL EPISODE	IN CASES IN WHICH NO DIAG- NOSIS NOTED ON HOSPITAL RECORDS, WHAT DIAGNOSIS WAS MADE FROM THE CLINICAL PICTURE?	BASED ON THE POSTMORTEM FINDINGS, WAS THE TREN- DELENBURG OPERATION FEASIBLE?	ASIDE FROM THE PULMO- NARY EMBOLUS, WAS THE CAUSE OF DEATH?
19	Non-operative	4½ hours	Circulatory collapse		No	Yes
20	3rd day	12 minutes	Acute cardiac failure		Yes	Yes
21	1st day	1 minute		Yes	Yes	No
22	11th day	35 minutes	Pulmonary embo- lism		Yes	No
23	Non-operative	30 minutes		Yes	Yes	No
24	4th day	13¾ hours		Yes	Yes	No
25	Non-operative	8 days	Coronary throm- bosis		Yes	No
26	Non-operative	30 minutes		Yes	No	No
27	22nd day	50 minutes		Yes	Yes	No
28	Non-operative	11½ hours	Pulmonary embo- lism? Cerebral embolism?		No	Yes
29	12th day	10 minutes		Yes	No	No
30	3rd day	15 to 20 min.		Yes	No	No
31	Repeated small emboli the 4th and 5th days	15 minutes	Cardiac failure		No	No
32	8th day	9½ hours	Pulmonary embo- lism? Coronary thrombosis? Par- oxysmal tachy- cardia?		Yes	No
33	5th day	1 hour	Pulmonary embo- lism		Yes	No
34	12th day	2¾ hours	Pulmonary embo- lism		Yes	No
35	10th day	Few moments		Yes	Yes	No
36	Non-operative	Gradual down- hill course		No	No	Yes
37	5th day	30 minutes	Pulmonary embo- lism		No	Yes

TABLE 8—Continued

	POSTOPERATIVE DAY OF THE FATAL PULMONARY EMBOLIZATION	INTERVAL BETWEEN FATAL EMBOLI- ZATION AND DEATH	CLINICAL DIAGNOSIS OF THE TERMINAL EPISODE	IN CASES IN WHICH NO DIAG- NOSIS NOTED ON HOSPI- TAL CHART, COULD IT HAVE BEEN MADE FROM THE CLINICAL PICTURE?	BASED ON THE POSTMORTEM FINDINGS, WAS THE TREN- DENBURG OPERATION FEASIBLE?	ASIDE FROM THE PULMO- NARY EMBOLUS, WAS THE CASE HOPELESS?
8	Non-operative	Gradual down- hill course		No	Yes	Yes
9	8th day	9 hours		No	No	No
0	2nd day	1 hour; 5 min.	Coronary throm- bosis? Pulmo- nary embolism?		Yes	No
1	Non-operative	Gradual down- hill course	Cerebral throm- bosis		No	Yes
2	8th day	10 minutes	Cerebral accident. Pulmonary embo- lism		No	Yes
3	7th day	1 hour	Pulmonary embo- lism		No	Yes
4	7th day	Few moments		Yes	?	Yes
5	10 weeks	Several days	Carcinomatous cachexia		No	Yes
6	Non-operative	Gradual down- hill course	Coronary throm- bosis. Heart failure. Pul- monary infarct		No	Yes
7	Non-operative	2 days		No	No	No
8	Non-operative	2 days	Pulmonary embo- lism? Perfora- tion of gastric carcinoma		No	Yes
9	5th day	2 hours; 20 minutes	Coronary throm- bosis		Yes	No
0	13th day	25 minutes	Pulmonary embo- lism		Yes	No
1	4th day	10 minutes	Pulmonary embo- lism		Yes	Yes
2	6th day	15 minutes	Pulmonary embo- lism		Yes	No
3	1st day	10 minutes	Pulmonary embo- lism		Yes	No
4	Non-operative	2 days	Subarachnoid bleed- ing? Coronary thrombosis?		Yes	Yes

TABLE 8—Continued

CASE NUMBER	POSTOPERATIVE DAY OF THE FATAL PULMONARY EMBOLIZATION	INTERVAL BETWEEN FATAL EMBOLIZATION AND DEATH	CLINICAL DIAGNOSIS OF THE TERMINAL EPISODE	IN CASES IN WHICH NO DIAGNOSIS NOTED ON HISTOPATHOLOGY, COULD IT HAVE BEEN MADE FROM THE CLINICAL PICTURE?	BASED ON THE POSTMORTEM FINDINGS, WAS THE TRENDLENBURG OPERATION FEASIBLE?	ASIDE FROM THE PULMONARY EMBOLUS, WAS THE CASE COMPLICATED?
55	9th day	11 days	Coronary thrombosis? Multiple pulmonary emboli?		No	No
56	10th day	15 minutes	Pulmonary embolism		Yes	No
57	18th day	35 minutes	Pulmonary embolism? Coronary thrombosis?		Yes	Yes
58	11th day	45 minutes		No	No	No
59	12th day	20 minutes		Yes	Yes	No
60	Non-operative	25 minutes	Coronary thrombosis		Yes	Yes
61	Non-operative	10 minutes	Hemorrhage into brain tumor? Coronary thrombosis?		Yes	Yes
62	4th day	10 minutes		Yes	No	Yes
63	59th day	Few hours		No	Yes	Yes
64	23rd and 40th days	14 hours after 2nd embolus	Coronary thrombosis		No	Yes
65	18th day	10 minutes		Yes	Yes	No
66	Non-operative	Few days	Coronary thrombosis		No	No
67	Non-operative	17 minutes	Pulmonary embolism		No	No
68	Non-operative	1½ hours		Yes	No	No
69	22nd day	15 minutes	Pulmonary embolism		Yes	No
70	10th day	3 days		No	No	Yes
71	Non-operative	4 hours		Yes	No	Yes
72	5th day	Rapidly downhill course postoperatively		Yes	No	Yes
73	3rd day	Rapidly downhill course postoperatively		No	No	Yes

TABLE 8—Continued

POSTOPERATIVE DAY OF THE FATAL PULMONARY EMBOLIZATION	INTERVAL BETWEEN FATAL EMBOLI- ZATION AND DEATH	CLINICAL DIAGNOSIS OF THE TERMINAL EPISODE	IN CASES IN WHICH NO DIAG- NOSIS NOTED ON HOSPI- TAL CHART, COULD IT HAVE BEEN MADE FROM THE CLINICAL PICTURE?	BASED ON THE POSTMORTEM FINDINGS, WAS THE TREN- DELENBURG OPERATION FEASIBLE?	ASIDE FROM THE PULMO- NARY EMBOLUS, WAS THE CASE HOPELESS?
Non-operative (1 mo. after compound fracture)	8 days	Cardiac or cerebral death		No	Yes
5th day	4 hours	Cardiac failure. Peritonitis?		Yes	No
Non-operative	Few minutes		No	Yes	Yes
Non-operative	Few minutes	Cerebral hemor- rhage. Cardiac collapse		Yes	Yes
9th day	10 minutes	Pulmonary embo- lism		No	No
8th day	15 minutes		Yes	No	No
Non-operative	2 days	Bronchopneumonia		Yes	No
15th day	45 minutes	Pulmonary embo- lism		?	No
5th day	2 days	Peritonitis? Pneumonia?		?	No
10th day	6 days		No	No	Yes
4th day	1 day	Bronchopneumonia		No	Yes
12th day	5 minutes	Pulmonary embo- lism		No	No
Non-operative	19 minutes	Cardiac failure? Pulmonary embo- lism?		No	Yes
17th day	40 minutes		Yes	Yes	Yes
15th day	Gradual down- hill course postopera- tively		No	No	Yes

Pulmonary emboli may be minute, so that they lodge in the small peripheral pulmonary arterial branches. While many such emboli may produce pulmonary infarctions, parenchymal changes do not necessarily follow, for, as shown by Holt (7), and Karsner and Ash (77), infarction will occur only if there is some obstruction to the return venous flow from the lung. Pulmonary emboli may occur through all gradations in size from minute clots to the other extreme

consisting of long, massive thrombi of wide caliber, occasionally with twig-like branches, suggesting casts of the veins in which they originated. Large thrombi usually are purplish-gray in color, friable, and often lamellated. They may be intact and twisted or coiled up in one or more of the major branches of the pulmonary artery, in the main pulmonary artery, or in the right ventricle at its outflow tract. In some cases these massive thrombi have become fragmented and may be found distributed throughout the pulmonary arterial tree. There is one instance (Case 29) in which there were six large emboli (each measuring 5-10 cm. in length and 5-7 mm. in diameter) extending from the inferior vena cava

TABLE 9

Interval Between the Onset of the Fatal Episode of Embolism and Death

"Few moments.....	3	18 patients died within 10 minutes	27 patients died within 15 minutes	38 patients died within 30 minutes	46 patients died within one hour	
1 minute.....	1					
2 minutes.....	0					
3 minutes.....	2					
4 minutes.....	0					
5 minutes.....	1					
6 to 10 minutes.....	11					
11 to 15 minutes.....	9					
16 to 30 minutes.....	11					
31 to 60 minutes.....	8					
1 to 2 hours.....	2	23 patients died within 1 to 24 hours after the fa- tal embolism.				
2 to 4 hours.....	10					
4 to 8 hours.....	4					
8 to 10 hours.....	2					
10 to 12 hours.....	1					
12 to 24 hours.....	4					
2 to 7 days.....	10					
2nd week.....	3					
3rd week.....	0					
Prolonged gradually downhill course. Time of embolism could not be determined.....	6					
Total.....	88					

through the right auricle, right ventricle, pulmonary conus and artery, right and left main pulmonary arteries, and into many of the intrapulmonic branches.

The length of time the emboli were lodged in pulmonary arteries must be estimated from the clinical picture, the degree of organization of the infarcts if any are present, and the degree of adherence of the emboli to the intima of the vessels. Apparently, as far as can be judged from the autopsy and clinical features, attachment between the emboli and the walls of the pulmonary arteries usually begins within a few hours. However, emboli may remain free and local accretion of fresh clot may take place on the surface and on the ends. Thus primarily incomplete embolic obstruction of either peripheral or central branches of the pulmonary circulation may be secondarily converted into a complete

and account for the delayed death of some patients who have survived one or more initial embolizations (illustrated by Cases 6 and 12).

From the picture of the pathology observed at autopsy it is apparent that emboli may arrive in the pulmonary circulation singly or in small groups, or a single embolization may occur when a shower of many emboli takes place, the result of the fragmentation of an initially large thrombotic mass.

Embolism of peripheral branches of the pulmonary arteries, leaving the main trunks free, may produce symptoms of marked severity and may even cause death (illustrated by Cases 68 and 77). On the other hand, a massive embolus may lodge in one or more of the major pulmonary arteries and yet not be immediately fatal, death occurring hours or even days later. Although it may be assumed that, when a patient survives a severe episode of pulmonary embolism, the lesion was a minor one, complete recovery may follow a major pulmonary embolism. Proof of this can be deduced from one of our cases (Case 11) in which the patient survived an initial severe episode, dying rapidly five days after a second massive embolism. At autopsy the first embolus, which the patient survived, was a large slightly adherent thrombus situated in both the right and left main pulmonary arteries. The second embolus was also large and was coiled up in the right ventricle and its outflow tract.

The Clinical Picture of Minor Pulmonary (Branch) Embolism. For purposes of comparison, as well as contrast, minor pulmonary embolization warrants brief consideration. Insofar as our series of 88 cases is concerned, minor embolization must be considered because it occasionally preceded major episodes. Small emboli may cause severe symptoms, but this would seem to be the exception rather than the rule. The symptoms of minor embolism usually begin with pain in the chest, occasionally precordial or substernal, but more often pleuritic in nature, its location corresponding to the pulmonary segment which is involved. Infarction at the diaphragmatic surface of the lung is usually accompanied by pain in the shoulder on that side. Associated with the pain there may be cough, dyspnea, rapid pulse and moderate fever. Hemoptysis, when it occurs, usually does not appear for 12 to 24 hours, and then may consist only of slight blood-tinging of scanty sputum. The latter symptom occurred in only 3 of our 43 patients in whom "primary" embolizations had occurred prior to the fatal episode. Thus, the classical combination of thoracic pain, cough and hemoptysis, and an afebrile state often is wanting. Severe manifestations may occasionally be present. These include fall of blood pressure, sweating, pallor and/or cyanosis, apprehension, dizziness, faintness and, in some cases, vomiting and abdominal pain. The latter two symptoms, on occasion, have been misinterpreted as indicating an intra-abdominal complication. In some of our cases typical symptoms, physical signs and x-ray evidence ascribed to postoperative bronchopneumonia were proven at necropsy to have been due to pulmonary embolism and infarction.

The Clinical Picture of Major Pulmonary (Main Trunk) Embolism. In those cases in which pulmonary embolism causes death, the clinical picture presents many variations in signs and symptoms. The variations are referable to the

complex pathologic-physiologic alterations that are initiated when one or more emboli invade the main pulmonary arterial circulation. As already noted in several theories, supported by clinical and experimental evidence, have been offered to explain the mechanism of death following pulmonary embolism. In repeat, these mechanisms consist of 1) asphyxia; 2) acute right heart failure; 3) reflex phenomena producing either vasomotor shock or inhibition of cardiac or respiratory centers; 4) obstruction of blood flow to the left heart causing reduction in its output, with consequent loss of circulatory blood volume. Secondary changes incident to these mechanisms produce the manifestations of right heart failure (acute cor pulmonale (79)) or left heart failure, peripheral circulatory collapse, cerebral anoxemia and insufficiency of the coronary circulation. The complexity of the clinical picture is further increased by the fact that in many cases, two (or more) mechanisms may operate simultaneously, and at the same time exert more or less influence upon each other.

Thus, massive (lethal) pulmonary embolism may be manifested by essentially one of several clinical pictures: asphyxia, shock, syncope or cardiac failure, or various combinations of these syndromes (illustrated by Cases 2, 3, 4, and 11).

It is often difficult clinically to state which mechanism or mechanisms are operative in a particular case because of the fact that many of the cardinal signs and symptoms may be attributed to more than one physiologic disturbance.

There is a widely held impression that death following pulmonary embolism usually ensues instantaneously or, at least, very rapidly. While it is true that a certain number of patients succumb within a few seconds or minutes, a considerable proportion of them survive for as long as several hours and even days (illustrated by Cases 5, 6, 10, and 12). The duration of the fatal episode in the patients in our series is recorded in Table 9, which warrants special attention because of therapeutic possibilities.

It should be noted that only 7 patients died within 5 minutes of the onset of symptoms. Nine patients died in from 11 to 15 minutes, 11 in from 16 to 30 minutes, and 8 in from 31 to 60 minutes. Thus, 18 patients died within 15 minutes, 27 within 15 minutes, and 38 within 30 minutes. In 46 patients the interval between the final embolism and death was within one hour. Of the remaining 42 patients, 23 died in 1 to 24 hours, 10 died in from 2 to 7 days, and 3 died in the second week. In 6 cases, the clinical picture was one of slow progressive deterioration, and it could not be determined from the clinical records or necropsy protocols when embolism had occurred.

From the correlation of the clinical features of the fatal episodes in our case with the pathologic findings at autopsy we have made the following observation which we believe to be basic. Contrary to reported experimental and clinical classifications of the clinical pictures in relation to peripheral and central pulmonary embolizations (e.g., asphyxia in embolism of peripheral branches and syncope in embolic block of the main pulmonary arteries), the analysis of our series reveals that there is no constant relationship between the degree, location and extent of the pulmonary embolism and the clinical syndrome produced. In other words, similar and even identical pathologic alterations in the pulmonary

arterial circuit may produce dissimilar clinical manifestations. Conversely, widely different embolic combinations may be associated with similar and even identical clinical pictures.

In our opinion the problem of the management of pulmonary embolism cannot be faced squarely unless the foregoing statement is fully appreciated. As we have indicated, the literature deals at length with many aspects of the problem but devotes scarcely any attention to the clinical features in relationship to the pathology of pulmonary embolism. It is essential to present the details of many cases in order to gain a rounded picture. Space does not permit the description of our 88 certified cases. We have, therefore, chosen examples to illustrate most if not all the varieties which were encountered. Comments are offered after single case reports or after groups of related cases.

(To be continued)

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ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

the Sheltered Workshop in the Rehabilitation of the Tuberculous. L. E. SILTZBACH. *Milbank Memorial Fund Quarterly*, 21: 1, 80, January, 1943.

Nine hundred and sixty-four ex-patients with pulmonary tuberculosis were admitted to the Altro Work Shops, a medically controlled garment factory, for a rehabilitation course between the years 1915-1939, and were followed to the closing date of the survey, July 1941. The longest period of follow-up medical observation was twenty-five years and the shortest, one and one-half years. Ninety-seven per cent of the workers were traced five years; 2 per cent could be traced ten years. All the workers had received some treatment before admission to the workshop. In the earlier period, 1915-1929, only 6 per cent of the patients received collapse therapy before Altro admission; in the later period, 1930-1939, 51 per cent had some form of collapse therapy.

The Coated Tongue. B. B. CROHN AND R. DROSD. *Gastroenterol.*, 1: 1, January, 1943.

The authors were 'stymied' in their attempt to explain simple coated tongue on a basis of direct retrogression of gastric or intestinal material. Under exceptional conditions, however, the retrograde transport of colonic content as far as the stomach was demonstrated. Coated tongues occur in persons who have abused their digestive tract rather than under conditions of fasting. It is felt that the concept of the coated tongue is an intrinsic phenomenon. Reflexly, through the anatomic nervous system, the tongue reflects the state of hydration of the body, the conditions of digestive activity in the intestinal tract and the general health of the individual.

Alkaptonuria with Hyperuricemia. A. LESLIE. *Arch. Int. Med.*, 71: 1, 69, January, 1943.

A case of alkaptonuria with hyperuricemia is presented. This is the first reported case in which these two conditions representing distinct metabolic disturbances have been co-existent. There was apparently no connection between the two disturbances, and laboratory studies and therapeutic studies failed to reveal any. Reduction in excretion of homogentisic acid was noted after the administration of ascorbic acid. It is probable that this was a secondary effect because, (a) ascorbic acid merely by virtue of its reduction properties can prevent darkening of the urine and (b) complete absence of homogentisic acid from urine was not achieved. Administration of ascorbic acid did not affect the blood level of uric acid. The mechanism of alkaptonuria with hyperuricemia is discussed.

Transitory Hemiplegia Associated with Hypoglycemia in a Diabetic Child with Congenital Heart Disease. A. E. FISCHER AND A. L. FLORMAN. *Am. J. Dis. Child.*, 65: 73, January, 1943.

A nine year old girl with congenital heart disease, clinically diagnosed as the tetralogy of Fallot, had been under treatment for diabetes for three years. She developed hemiplegia on several occasions. Differential diagnosis lay between recurrent cerebral thrombi or angiospasm, and severe reactions to insulin in a child whose circulation was impaired.

Complications and Causes of Mortality of the Surgical Treatment of Carcinoma of the Colon and Rectum. J. H. GARLOCK, L. GINZBURG, AND A. GLASS. *Surg., Gynec. & Obst.*, 76: 51, January, 1943.

The authors find that complicating medical conditions influence to a large extent the

morbidity and mortality of colonic surgical procedures. A prominence of the pre-operative period of rehabilitation in these cases should minimize the affects of these complicating illnesses. In the reported series, operability has been influenced more by conditions associated with the growth itself than by the age of the patient, obesity, anemia, etc. Fecal perforation of a carcinoma of a colon is a fatal complication in most instances. The pre and post-operative use of the Miller-Abbott tube is emphasized. The pre-operative use of sulfanilamide has distinctly decreased the incidence of wound infections and peritonitis; the value of its local use is equivocal. The post-operative pulmonary complications have been benefited by the sulfa drugs. Cardiovascular complications constitute the major cause of post-operative mortality. The buried alloy steel wire has tended to eliminate wound disruption. Retraction of a loop of bowel within the abdomen following colostomy is a serious complication and usually fatal. Obstructive resection and wide excision of the mesentery for neoplasm of the transverse and left colon has been found to be a relatively safe procedure. The one stage abdominoperineal resection is preferred for carcinoma of the rectum. Failure to recognize rectal neoplasms early is stressed and the authors call attention to the fact that between 20-25 per cent have undergone treatment for hemorrhoids during the preceding 2-5 months.

Hemolytic Reactions as a Result of Isoimmunization Following Repeated Transfusions of Homologous Blood. P. VOGEL AND N. ROSENTHAL. *Am. J. Clin. Path.* 13: 1, January 1943.

Severe hemolytic reactions following repeated transfusions of homologous blood in sickle cell patients have been shown to be due to the Rh-agglutinin. In four patients the anti-Rh agglutinin was demonstrated. In the seventh patient a cold agglutinin with a wide range of temperature activity not related to the Rh factor may have been responsible for the reaction.

Alopecia from Cyverine Hydrochloride. L. LEVIN AND H. T. BEHRMAN. *J. A. M. A.*, 118: 41, January, 1943.

A white woman aged 49 years ingested 920 mg. of cyverine hydrochloride, an antispasmodic drug, within a period of thirty days. At the end of this time alopecia of the scalp developed. This was progressive and resulted in approximately the complete loss of hair from the scalp. The eyebrows and eyelashes turned a grayish white shortly after the occurrence of alopecia. There was an associated exfoliative dermatitis of the skin and a diminution of perspiration.

The suggestion is advanced that the effects of the drug on smooth muscle caused complete relaxation of the erector pili muscles around the hair follicles. In this manner loosening of the hair shaft and subsequent alopecia may have occurred.

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THE PHYSIOLOGY OF THE ADRENALS*

LOUIS J. SOFFER, M.D.

The history of the physiology of the adrenals dates back to the original clinical and pathological observations of Addison (1) concerning the effects of destructive disease of the adrenal glands. These observations represented the first concrete evidence that these glands, particularly the cortex, were organs which were essential to life. This observation was promptly confirmed experimentally by Brown-Séquard one year later (1856), who extirpated the adrenals from a number of laboratory animals. The rapidly fatal outcome of these experiments confirmed Brown-Séquard (2) in the impression that these organs were indispensable to life.

It is interesting that a period of almost 300 years intervened between the original description and identification of these glands by Eustachius (3) and their recognition as important clinical and physiological entities. Not that these three centuries were devoid of thought dealing with the suprarenal bodies, but clinical and physiological investigation was of necessity limited, and the significance of these small organs was distorted and frequently disregarded. The fantastic theories which were elaborated concerning their function varied from the conception of Spigelius (4) that they served as mere fillers of the abdominal cavity to help support the stomach, to the equally startling hypothesis of Molinetti (4) that the adrenals diverted the blood from the kidneys in order to avoid the excretion of urine by the fetus. In any event, the work of Addison served to create a sense of reality and meaning to the adrenals, and established them as organs of clinical significance.

Our present knowledge of the functions of these glands is based to a considerable extent on the clinical distortions associated with adrenal disease, and it may be worth while to review this clinical background in a general broad way.

For half a century and more after Addison's classic description, efforts were directed to clinical and pathological studies of the diseases of the adrenal. It was promptly realized that the adrenal cortex and medulla were in reality distinct organs with separate developmental histories. As a matter of fact, in some of the lower forms of life the cortical and medullary tissue are not fused but remain separate and apart. The cortical tissue of the adrenal is derived from the mesoderm, and is closely associated with the urogenital mass. It is for this reason that adrenal cortical tumors so frequently and startlingly affect the secondary sexual characteristics. The medullary tissue, on the other hand, is derived from the ectoderm, and has a common origin with the cells constituting the sympathetic nervous system. Certain cells of the celiac plexus migrate from the medial side of the cortical anlage of the adrenal into its centre. These cells are called "sympathagones" and they constitute the building cells

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both of the adrenal medulla and of the sympathetic nervous system. The sympathagones are, therefore, an early undifferentiated form of cell. Further development of the sympathagones occurs along two lines. They will give rise to a slightly more differentiated cell, the "sympathoblast" on the one hand and the "chromophiloblast" on the other. The "sympathoblast" will differentiate further into the "neuroblast" and finally into a mature ganglion cell or sympathetic neuron, while the chromophiloblast will differentiate into the mature chromophil cell. Since the "sympathogone" has its origin from the embryonic sympathetic nervous system, the more differentiated cells derived from it are found wherever sympathetic nervous tissue is present. It is important to bear this in mind, since tumors of these cells may have their origin not only in the adrenal medulla but in those various parts of the body where these cells develop.

With this brief embryological background, we can classify adrenal disease essentially as follows:

- A. Destructive lesions of the adrenals, such as
 - 1. Tuberculosis
 - 2. Atrophy
 - 3. Hemorrhage

} Producing the clinical picture of Addison's disease
- B. Tumors of the adrenal medulla and sympathetic ganglia
 - 1. Sympathogonioma—arising from the undifferentiated sympathogones
 - 2. Sympathoblastoma or neuroblastoma—consisting of somewhat more mature and differentiated types of cells
 - 3. Ganglioneuroma—composed chiefly of mature ganglion cells and nerve fibers
 - 4. Chromaffinoblastoma—consisting of an undifferentiated type of cell, the precursor of the chromaffin cell
 - 5. Chromaffinoma—consisting predominantly of the chromaffin cells of the adrenal medulla
 - 6. Paraganglioma—consisting of extra-adrenal chromaffin cells having their origin in the paraganglia
- C. Tumors of the adrenal cortex
 - 1. Without virilism
 - 2. With virilism
- D. Hyperplasia of the adrenal cortex
 - 1. With virilism

The tumors of the adrenals may be roughly divided into those with and those without endocrinological significance. Thus, the sympathogonioma, neuroblastoma, and ganglioneuroma produce no undue hormonal secretions. The sympathogonioma and neuroblastoma are malignant tumors whose clinical significance is related to their malignancy and associated metastasis, while the ganglioneuroma, which is composed of highly differentiated and mature cells, is essentially a benign and innocuous tumor usually discovered accidentally at necropsy. The chromaffinomas, paragangliomas, and adrenal cortical tumors

with virilism, on the other hand, exercise their effects mainly through the secretion of excessive amounts of hormone or hormones and the attendant clinical picture is conditioned by this endocrinological abnormality. The destructive lesions of the adrenal cortex, finally, represent a state characterized by a failure of hormone formation with the development of a characteristic clinical picture.

This, then, represents the clinical background against which subsequent physiological observations were made. The first significant report was that of Vulpian (5) who noted a green coloration which occurred when the adrenal medulla was moistened with a dilute solution of ferric chloride, and it was promptly realized that some substance, the exact significance and nature of which was not known at the time, but which had a catechol nucleus, was being secreted by the adrenal medulla. In 1894, Oliver and Schaefer (6) demonstrated the remarkable blood pressure rise which followed the injection of an extract of the adrenal medulla. Some eight years later, Abel (7) succeeded in isolating a crystalline compound from the adrenal gland, which he considered to be its active principle and which he called "epinephrine."

The origin of epinephrine in the body is obscure. The close structural similarity which epinephrine bears to both tyrosine and phenylalanine would suggest that either of the latter two amino acids may be converted to epinephrine. Actually such a transformation can occur in the testube through the successive processes of oxidation, methylation of the nitrogen atom, and decarboxylation, but in vivo experiments have failed to confirm the conversion of either tyrosine or phenylalanine into epinephrine. However, Nikolaeff (8) demonstrated that the perfusion of the isolated adrenal with a solution containing tyramine results in the formation of a substance having the properties of epinephrine. This was subsequently confirmed by Schuller and Wiedemann (9) who found, in addition, that tyramine is formed in the kidney by decarboxylation of tyrosine.

The physiology of the adrenal medulla is essentially a study of the pharmacology of epinephrine. Since the isolation and identification of this hormone a voluminous literature has accumulated, dealing with its properties and actions. It would serve no purpose other than that of recapitulation to recount these studies in detail in this lecture. However, certain aspects are worth reemphasizing. Despite our extensive knowledge of the actions of epinephrine, its actual function in the body economy is obscure. That the medulla, the main source of epinephrine formation, is not indispensable to life is evidenced by the fact that the totally adrenalectomized animal and the patient with Addison's disease will continue to live and thrive provided adequate cortical hormone therapy is administered. One cannot assume that in the event of destruction or extirpation of the adrenal medulla, its functions are taken over by the extramedullary chromophil tissue. The latter at best secretes only minute amounts of epinephrine, and the adrenalectomized rat in which there is no extramedullary chromophil tissue continues to live and grow when treated with potent cortical extracts. Certainly, the laboratory effects of epinephrine on vascular tonus,

carbohydrate metabolism and its "emergency function" as elaborated by Cannon (10) are well documented and well observed phenomena. But the vascular tone of the adrenalectomized animal is promptly restored when treated with potent cortical hormones, while disturbances in carbohydrate metabolism and the loss of "emergency response" are corrected by certain fractions of adrenal cortical extract. Nevertheless, it is inconceivable that a substance as pharmacologically active as epinephrine does not play a very significant role in the body economy. Grollman (11) has suggested that its major function is to protect or act synergistically with the more vital and destructible cortical hormone. The evidence adduced for this hypothesis is, however, meager and at best decidedly equivocal.

The development of an operative procedure within recent years for the treatment of hypertension has again raised the question of the significance of the adrenal medulla and extramedullary chromophil tissue. The rate of secretion of epinephrine is readily affected by impulses from the splanchnic nerves, and it is a not unreasonable assumption that these nerves normally control the rate of such secretion. Feldberg and his coworkers (12) have probably correctly concluded that the action of the splanchnic impulses is mediated through acetylcholine, which acts as a humoral transmitter. Sympathectomy and splanchnicectomy, the operative procedure of choice, certainly produces a fall in blood pressure, but this is essentially transient, since in the large majority of instances hypertensive levels are again subsequently attained. The further significance of these clinical experiments lies in the fact that these patients manifest no undue physiological aberrations which can be attributed to adrenal medullary insufficiency. However, the antithesis of this was observed in patients with pheochromocytoma and paraganglioma. With the development of our knowledge of the actions of epinephrine, the clinical picture associated with such tumors became clear. It was evident that the characteristic signs and symptoms, the episodes of nervousness, trembling, sweating, and pallor, periods of paroxysmal severe hypertension, and hyperglycemia and glycosuria were due to the secretion and liberation of excessive amounts of epinephrine.

One further point about the metabolism of epinephrine may be worth considering, and that is the role that it plays in pigmentation. This is of course, particularly significant in Addison's disease, where one of the classical features of this disease is the development of extensive pigmentation of the skin due to melanin. Brown-Séquard suggested that a precursor of adrenalin is transformed into melanin. Block (13) demonstrated that an isolated piece of skin if soaked in dioxypheylalanine (Dopa solution) becomes darkly pigmented. He then advanced the hypothesis that pigmentation is due to the presence of a specific oxydase in the skin, which forms melanin from dioxypheylalanine. This substance may be a normal precursor of adrenalin, and since it is not converted into adrenalin as rapidly as usual, due to adrenal disease, the dopa becomes fixed in the skin and is then converted to melanin through the action of the enzyme dopase.

This ingenious hypothesis concerning the formation of melanin has some chemical basis in fact. Barger (14) has shown that tyrosine is converted to

5-hydroxyphenylalanine which on further oxidation yields an indole carboxylic acid which can be transformed into dihydroxyindole. This compound in turn may be condensed to a black pigment similar to the melanin of the skin. Neureg (15) demonstrated that epinephrine, too, may be oxidized in the presence of certain oxidases to yield a black pigment similar to melanin. In view of these reactions, it has been assumed that epinephrine, tyrosine, phenylalanine, and 5-hydroxyphenylalanine are precursors of melanin.

However, this does not clarify the role that the adrenal plays in the excessive deposition of melanin in Addison's disease. Since pigmentation occurs both in a tuberculous disease of the adrenals, where both the cortex and medulla are destroyed, and in Addison's disease, due to atrophy of the cortex, where the medulla is relatively intact, one finds it difficult to assume that the latter plays a vital part in pigmentation. Similarly, it is difficult to understand what role the cortex plays in this process, since the administration of whole cortical extracts or the various fractions thereof do not affect the pigmentation of Addison's disease to any remarkable extent. To further confuse the picture, classical instances of Addison's disease with the usual post-mortem findings are reported, in which no undue pigmentation was present during the entire prolonged course of the disease. It is noteworthy, too, that in no bilaterally adrenalectomized animal has any undue deposition of pigment in the skin been observed. One must conclude that at present the pathogenesis of the pigment melanin, at least in Addison's disease, is still obscure.

The demonstration and identification of epinephrine as an adrenal medullary hormone unquestionably represented a great step forward in our understanding of the physiology of the adrenals. But, in a sense, it served to retard further studies dealing with adrenal physiology for a considerable period of time. With the interest attached to the discovery of epinephrine, the possibility of the existence of other adrenal hormones was lost sight of until the middle 1920's. It was only after extensive therapeutic trials and failure of epinephrine in Addison's disease that it was realized that this hormone by no means represented the vital hormone of the adrenals, and further study of adrenal function was thus stimulated.

One may state unhesitatingly that the adrenal cortex is indispensable to life. That it secretes a number of hormones, the exclusion of which, from the body of man or of animals, results in a rapidly fatal outcome. During the past two decades, considerable advances have been made both in our understanding of the physiology of the adrenal cortex and our knowledge of the elaboration of its hormones.

The physiology of the adrenal cortex is intimately concerned with

- (1) Electrolyte metabolism
- (2) Carbohydrate metabolism
- (3) Renal function
- (4) Growth of young animals
- (5) Resistance to stress
- (6) Relation to blood pressure, and
- (7) Muscular response

RELATION OF ADRENAL CORTX TO ELECTROLYTE METABOLISM

The first observations dealing with the inorganic serum constituents were made by Lucas (16) and by Rogoff and Stewart (17). Lucas noted a low chloride level in the blood of adrenalectomized dogs. In the same year, the latter investigators reported similar findings. In 1927, approximately one year later Bauman and Kurland (18), working with adrenalectomized cats under ether anaesthesia, observed a drop in the proportion of plasma during adrenal insufficiency, and an increase in the plasma solids. They found that there occurred a 15 per cent fall in the plasma concentration of the sodium ion, and a 9 per cent reduction in that of chloride. They also observed an elevation in the plasma potassium and magnesium concentration. Hastings and Comper (19) emphasized the considerable increase in serum potassium which may occur during insufficiency in the adrenalectomized dog.

In 1932, Loeb (20) observed an unusually low concentration of sodium and chloride in the serum of three patients with Addison's disease. These observations were promptly confirmed by Harrop and his coworkers (21, 22) both in the bilaterally adrenalectomized animal and in patients with Addison's disease. It was then found that these patients, as well as the adrenalectomized animals could be maintained without the use of cortical extract, provided they were maintained on a high intake of sodium chloride with an excess of sodium ion and a low potassium intake (23, 24, 25). This represented the first of a series of studies elaborating the relationship of the adrenal cortex to salt and water metabolism. The sequence of events that occurs in the crisis of Addison's disease and in the bilaterally adrenalectomized animal may be essentially described as follows: The initial change that occurs is a loss of sodium and chlorides in the urine. The sodium ion is intimately concerned with water metabolism, and is present in the intercellular fluid in isotonic concentration. The excretion of sodium carries with it a certain amount of water, each milliequivalent of sodium being excreted approximately with 6.5 cc. of water. The significance of this can be gauged if we bear in mind that in untreated adrenal cortical insufficiency there is a daily negative sodium balance of about 50 to 100 milliequivalents. Translated in terms of water balance, it would mean that such a patient loses daily 300 to 650 cc. of water above his normal daily fluid loss.

It is important to consider the site of origin of this fluid, and the disturbance in the internal milieu which occurs as a result of it. Gamble (26) has pointed out that the fluids in the body are present essentially in two compartments, the extra-cellular fluid, which comprises about 20 per cent of the body weight, and the intra-cellular fluid, which represents about half the body weight. The electrolytic content of these two compartments is quite different, although the osmotic pressure on both sides of the cell membranes remains fairly equal. The extra-cellular fluid is a blood dialysate, essentially protein free, and its major ionic base is sodium. The acid ions, chloride, bicarbonate, organic acids, and minute amounts of protein exercise practically no effect on the osmotic pressure, and their ionic concentration is automatically regulated through respiration and renal excretion, to equal that of the total base. In

the extra-cellular fluid, therefore, the sodium determines the osmotic pressure. In the intra-cellular fluid, on the other hand, the major base is the potassium ion, while the acid ions consist of phosphates, bicarbonate, sulphates, and protein. The exchange of water between the cells and the interstitial spaces is determined and regulated by the osmotic pressure on each side of the cell membrane. The volume of the blood plasma tends to remain constant under normal circumstances, despite variations in fluid intake, at the expense of the interstitial fluid, the latter acting as a reservoir which adds fluid to or removes it from the plasma as the needs dictate. However, when the volume of the extra-cellular fluid is materially decreased, this will be reflected in a corresponding decrease in the plasma volume, as the latter contributes its fluid stores to the interstitial spaces in an attempt to maintain the internal milieu intact. In adrenal cortical insufficiency, the salt and water lost in the urine comes primarily from the extra-cellular fluid. This depletion of the sodium ion results in a decrease of the osmotic pressure of the interstitial fluid relative to the cell. In an effort to maintain equal osmotic relationships, fluid migrates from the interstitial space into the cell, thus further depleting the fluid stores from the former compartment. Because of the character of the cell membrane, osmotic relationships cannot be adjusted by migration of ions out of the cells into the interstitial spaces. The dehydration so characteristic of adrenal insufficiency occurs, therefore, on at least two bases—the loss of salt and water from the extra-cellular fluid in the urine, and the further loss of fluid from the tissue spaces into the cell. With a progressive loss of inter-cellular fluid, there then occurs a decrease of blood volume. These changes, if uncorrected, go on to the development of shock. It is this picture of shock which we speak of as an Addisonian crisis.

The loss of sodium and chloride in the urine in adrenal insufficiency was readily susceptible of proof, but the loss of fluid from the tissue spaces into the cells was more difficult to demonstrate. Harrison and Darrow (27) approached this problem by analysing muscle tissue obtained from both adrenalectomized and normal animals, and found that with a decrease in the sodium content of the extra-cellular fluid there occurred an increase in the fluid content of the cells. This hypothesis is further borne out by some experimental observations made by Harrop and his coworkers (28) in bilaterally adrenalectomized dogs. They observed that in these animals dehydration, hemoconcentration, and shock will occur even though a negative water balance is prevented by increasing the fluid intake. Since excessive fluid in these experiments is not lost through diuresis, and since dehydration and hemoconcentration nevertheless ensue, some redistribution of body fluids must occur to account for these phenomena. In another series of experiments, Harrop and his coworkers (29) showed that, following the administration of cortical extract to the adrenalectomized dog in insufficiency, there occurred a secondary diuresis. This was associated with an increased urinary excretion of potassium, phosphates, and urea. This potassium diuresis probably represents an excretion of intracellular fluid due to both cell shrinkage and cell destruction, as evidenced by the negative nitrogen balance during this period. During the period of secondary diuresis, the experimental animals' clinical condition has considerably improved and there has

occurred an increase in the plasma concentration of sodium and chloride ion. Another approach to this same problem was attempted by Swingle and his associates (30). They observed that the typical signs and symptoms of crisis occurred in anuric bilaterally adrenalectomized animals from which cortic extract was withheld. These animals obviously could not have lost any sodium in the urine, but none the less dehydration and shock occurred.

One further channel to account for fluid loss in adrenal insufficiency must be considered, and that is loss through the intestinal tract through vomiting and diarrhea. Both in the patient with Addison's disease and in the bilaterally adrenalectomized animal, vomiting and diarrhea do not occur until adrenal insufficiency has become well established. Dehydration, hemoconcentration and shock are already well developed when the disturbing gastrointestinal symptoms manifest themselves. These symptoms, with their associated loss of sodium and chloride ions unquestionably contribute to the final collapse, but do not account for the progressive and severe fluid loss seen early in adrenal insufficiency (22). The adrenal cortex, however, does play a part in the degree of absorption of sodium and chloride ions from the intestinal tract. Thus, in the adrenalectomized dog, withdrawal of adrenal cortical extract produces a marked decrease in the rate of absorption of sodium, chloride, and potassium ions from loops of the ileum. When extract is again administered, this trend is reversed (31). In early insufficiency, then, there is not only present an excessive loss of sodium and chloride, but a decrease in absorption of these ions and hence fluids from the intestinal tract.

RELATIONSHIP OF THE ADRENAL CORTX TO POTASSIUM METABOLISM

It is established that the adrenal cortex plays a primary and vital rôle in the metabolism of sodium. But whether it plays an equally significant rôle in the metabolism of potassium, or whether the latter is disturbed in adrenal cortical disease only secondary to alterations in the metabolism of the other electrolytes and in renal function is not quite so clear.

Potassium is essentially an intracellular ion, and the total content of the human body has been variously estimated as averaging about 0.25 per cent. The body of a 70 kilogram man, then, contains about 175 grams of potassium. Of this total, the extracellular spaces contain 3 grams, the blood plasma 0.3 grams, the blood 8 grams, and the remaining 164 grams is distributed in the various cells of the body, mostly the liver and muscles (32). The body cells in general are fairly permeable to potassium, as indicated by the injection of radioactive isotopes of this ion (33). However, under normal circumstances, potassium remains within the cell mostly because the cell membrane is impermeable to sodium and to all anions with which the potassium is combined other than the monovalent ones (34). Generally speaking, potassium moves from the cell into the plasma in those conditions involving excessive loss of sodium and water from the body, such as occurs in severe hemorrhage, shock, adrenalectomy, intestinal obstruction, etc. (32). The function of potassium in the body economy is by no means clear. That it plays some rôle in muscular activity is indicated by the fact that such activity results in a loss of potassium in the cell in exchange for sodium. This loss of potassium is in some way related to

the contractile process of muscle or their immediate recovery phase rather than acting as an agent in neuromuscular transmission of excitation. However, although it does not act as a humoral agent for neuromuscular transmission, it nevertheless plays an important part in the neuromuscular synapse. This is emphasized by the fact that potassium injections will reestablish contractions from nerve stimulation in a muscle that has previously been paralyzed by urare (35). This effect on the neuromuscular function explains its beneficent influence in the treatment and prevention of episodes of familial periodic paralysis (36). There is some evidence, too, of a relationship between carbohydrate and potassium metabolism. It apparently follows the carbohydrate cycle from muscle to liver and the reverse. It frequently rises and falls with the lactic acid level, as in exercise and shock. It is affected by insulin and adrenalin in essentially the same way that glucose is (32). Potassium may be concerned with the production of phosphoric acid esters (37), although the question as to whether it activates the process of phosphorylation or the breakdown of hexose-phosphate (38) is unsettled.

In adrenal cortical insufficiency, there occurs an elevation of the serum potassium. This increase in concentration is associated with a decrease in the urinary excretion of potassium, while the direct antithesis of this holds for the sodium ion. With recovery from adrenal insufficiency, there is an increase in the urinary excretion of potassium, a decrease of that of sodium, a concomitant fall in the serum potassium concentration, and a rise in serum sodium. The increase in the serum concentration of potassium observed during adrenal cortical insufficiency is associated with an increase in the potassium content of the intercellular fluid and of the cells (27), probably due to the failure of the kidneys to excrete adequate amounts of this ion.

The behaviour of the potassium ion in acute adrenal insufficiency as just described, does not of itself point to any primary and fundamental relationship to adrenal cortical function. The alteration in concentration of serum potassium may be secondary to the excursion of the sodium ion and water during insufficiency and after recovery. A similar situation prevails in acute hemorrhage and in shock, where adrenal cortical disease cannot be postulated. The evidence advanced in favor of a direct relationship between the adrenal cortex and the metabolism of potassium is based on the following observations: Ingle and his co-workers (39) have found that after bilateral nephrectomy in adrenalectomized rats, the administration of adrenal cortical extract can still cause an appreciable fall in the concentration of potassium in the serum. Further evidence was obtained from direct analysis of the tissues of adrenalectomized animals for potassium, in which it was observed that there was an increase in the potassium concentration of the intracellular muscle fluid. Administration of cortical extract reduced the elevated level of muscle potassium to normal values (27). Finally, the administration of desoxycorticosterone to normal dogs eventually induced a drop in the serum potassium to almost half the control level, and symptoms resembling those of familial periodic paralysis developed. These symptoms could be relieved by the withdrawal of the hormone or the administration of potassium chloride (40).

THE RELATIONSHIP OF THE ADRENAL CORTEX TO RENAL FUNCTION

Acute adrenal insufficiency is associated with marked disturbances in renal function. These disturbances are related to the dehydration, reduction in blood volume, and blood pressure, and are characterized by an elevation in the non-protein nitrogen. This general picture of renal failure, however, is indistinguishable from that observed in severe hemorrhage, dehydration, or shock from any cause, and is referred to as extra-renal azotemia. The extra-renal azotemia, whether due to adrenal failure or other causes of dehydration and shock is reversible by suitable therapy, and hence is essentially of a temporary character.

There is, however, another aspect of this problem of equally pertinent significance, and that is the relation of the adrenal cortex per se to renal function. This consideration is of fundamental importance, since it raises the question of the site of action of the adrenal cortical hormones. Shall we consider that the site of action of these substances is primarily on the kidney cells and that the entire train of events observed in the development of acute adrenal insufficiency is due to absence of such specific hormonal effect on the kidney cells? Or can we interpret the evidence of renal failure as part of the general picture associated with adrenal cortical insufficiency and lacking a primary and specific relationship to adrenal cortical function? This problem is difficult to answer. The first and most obvious approach is an anatomical one. Necropsy findings in patients with Addison's disease and in bilaterally adrenalectomized animals fail to reveal any consistent pathological alterations in renal structure. Guttman (41) in an analysis of 566 autopsied cases collected from the literature, found that less than 10 per cent showed alterations in renal morphology sufficient to justify an anatomic diagnosis of kidney disease. Barker (42) reported the autopsy findings in 28 cases of Addison's disease, and found that 10 showed definite anatomical changes in the kidney. The changes observed were mostly that of tubular atrophy with a flattening of the epithelium and diminution in the amount of cytoplasm. Talbott and his co-workers (43) studied the kidneys of 6 patients with Addison's disease who came to autopsy, and found no renal anatomical abnormalities. These results are similar to those in experimentally adrenalectomized animals in which no significant histologic changes were evident in the kidneys (44).

We can conclude from these pathological studies that the kidneys of patients with Addison's disease, or those of adrenalectomized animals, show no consistent or significant alteration in renal structure. However, the absence of gross or microscopic structural change does not exclude possible impairment of renal function specifically related to the lack of adrenal cortical activity. This phase of the problem could only be investigated with advantage during intercritical periods when the patients with Addison's disease and the adrenalectomized animals were relatively well.

The investigation of renal function with the usual clinical procedures, such as the determination of maximum urinary specific gravity, the presence of albuminuria, and the appearance of red blood cells and casts in the urinary sediment, as well as the non-protein nitrogen concentration in the blood and the

phenosulfonphthalein excretion do not reveal any constant deviation from the normal in these instances. It is essential to study specifically glomerular filtration and tubular absorption in order to determine the presence or absence of the more subtle alterations in renal function. Talbott and his co-workers (43) conducted such studies on 10 patients with Addison's disease when they were relatively well, had a normal blood electrolyte pattern, and were maintained only on supplementary oral salt therapy. The rate of formation of glomerular filtrate was determined by inulin clearance, and was found to be definitely reduced in every instance investigated. When these studies were repeated following the administration of desoxycorticosterone acetate or whole adrenal cortical extract there occurred a significant increase in the rate of formation of glomerular filtrate, although normal levels were never obtained. The question promptly presents itself as to whether the depression of the rate of glomerular filtration may not be due to a reduction in blood flow rather than to a specific alteration in glomerular function. The results obtained with creatinine and diodrast clearance studies at low iodine plasma levels suggested that the depression of the rate of glomerular filtration is out of proportion to the reduction in renal blood flow. Similarly, the observations of these authors on the maximum ability of the tubules to excrete diodrast and reabsorb glucose suggest that the tubular excretory function is well maintained while their ability to reabsorb, at least as far as glucose is concerned, is seriously impaired.

The relationship of renal function to water, sodium, and potassium clearances is of more practical and immediate importance in a study of the adrenal cortex. Talbott and his co-workers (43) found that there was no significant alteration in the tubular reabsorption of water either before or after adrenal cortical hormone therapy. Similarly, no dissipation of sodium was apparent while there occurred a definite increase in potassium excretion following treatment with potent cortical extracts. This increase in urinary potassium excretion was produced mainly by an increase in glomerular filtration. These results are in contrast to those obtained in adrenalectomized animals by Harrison and Darrow (45). These investigators found that the sodium clearance was increased while that of potassium was decreased when treatment with adrenal cortical extract was discontinued. Resumption of hormonal therapy promptly restored these clearances to normal. The observations of Harrison and Darrow (45) are probably correct, in view of the nature of the electrolyte changes which occur in adrenal insufficiency and the known clinical and laboratory response of the blood electrolytes to specific hormone therapy.

It is desirable at this point to summarize the relationship of the adrenal cortex to electrolyte and water metabolism and renal function. The conclusions to be drawn are based on the studies of the pathological physiology of the adrenal cortex. As to whether they apply to the physiology of the adrenal cortex under normal circumstances is at present impossible to know with any degree of certainty. In any event, disease or extirpation of the adrenals results primarily in an increase in the urinary excretion of sodium. This is associated with a loss of water resulting in a depletion of the intercellular fluid. At the same time, fluid is further lost from the extra-cellular tissue spaces by its migra-

tion into the cells. This depletion of extra-cellular fluid eventually results in reduction in the circulating plasma volume. When these factors become great enough, dehydration and shock are produced. Associated with an increase in the loss of sodium, there occurs a loss of chloride, although to a somewhat lesser extent, and a decrease in the urinary excretion of potassium with a consequent increase in the serum concentration of this ion. The fact that more sodium than chloride is lost plays a part in the acidosis which is always seen in the adrenalectomized animal in insufficiency and frequently observed during crisis of Addison's disease in man. The dehydration and shock induced by the salt and water loss, with the consequent reduction in renal blood flow and pressure, produces renal failure due essentially, therefore, to extra-renal factors. This entire process can be promptly reversed by the administration of adrenal cortical hormone. Under the influence of this therapy there occurs a decrease in the urinary excretion of sodium and chloride and an increase in excretion of potassium with a resultant elevation of the blood sodium and chloride levels and reduction in potassium concentration. With the retention of sodium, the inter-cellular fluid and the blood volume are replenished, and the cellular fluid is decreased. Although the major alterations in the metabolism of potassium are secondary to those of sodium, there is some evidence to indicate that the adrenal cortex exercises some specific effect on potassium metabolism. Similarly, the major renal functional alterations are secondary to the dehydration and shock which occur as a result of the sodium and water loss. But here, too, there is evidence to indicate that the adrenal cortex plays a specific rôle, although not of a very great magnitude, on the renal clearances of sodium and potassium.

The fact that patients with Addison's disease and the adrenalectomized animals are incapable of retaining sodium can be used as a test of adrenal cortical destruction (21). Thus, the administration of a salt-free diet to patients with Addison's disease or to adrenalectomized animals will induce a negative sodium balance, a rapid depletion of intercellular fluid and sodium, a drop in blood sodium and hemoconcentration and dehydration, and within a short period of time will precipitate acute adrenal insufficiency. The individual or animal with intact adrenals when subjected to salt deprivation will respond with a marked reduction in urinary sodium excretion so that no depletion, either of fluid or sodium, of the intercellular spaces or blood occurs for a prolonged period of time.

RELATION OF THE ADRENAL CORTEX TO CARBOHYDRATE METABOLISM

During the early period of investigation on the functions of the adrenal cortex, attention was concentrated mainly on its effects on electrolyte metabolism. The relationship of the cortex to carbohydrate metabolism was a source of great conflict between those groups who insisted that the carbohydrate disturbances observed in the adrenalectomized animals were fundamentally related to destruction of the adrenal cortex, and their opponents who postulated that these disturbances were non-specific in character and rather related to the malnutrition, so commonly present in the adrenalectomized animal. To some extent this difference in opinion concerning the significance of the disturbances

in carbohydrate metabolism was due to differences in behaviour of the adrenalectomized animals used. As Long, Katzin, and Fry (46) have pointed out, in some species overwhelming changes in electrolyte metabolism occur so promptly as to obscure any alterations in carbohydrate metabolism. In others, the animal survives long enough to permit these changes to become manifest.

It had been known for a long time that changes in carbohydrate metabolism do occur in the presence of destruction of the adrenal cortex. Porges (47) as early as 1910, pointed out the frequency with which hypoglycemic episodes occurred in patients with Addison's disease, and that similar episodes occurred in adrenalectomized dogs. And in 1925, which still represented the very early phase of the enlightened period in adrenal physiology, Marañón (48) demonstrated that patients with Addison's disease were markedly sensitive to minute amounts of insulin. With the advent of a potent cortical extract, the character of these carbohydrate disturbances could be more carefully evaluated. Britton and Silvette (49) were the early proponents of the significant and fundamental character of the changes in carbohydrate metabolism. They demonstrated the occurrence of hypoglycemic seizures in adrenalectomized guinea pigs, cats, and other species, phenomena not so readily observable in the adrenalectomized dogs. They further found that the liver and muscle glycogen of the adrenalectomized animals were considerably reduced, and that the ability of these animals to form liver glycogen from injected dextrose or sodium lactate was diminished. These observations received some clinical substantiation by Levy-Simpson (50), who demonstrated that patients with Addison's disease failed to show a rise in the blood sugar level comparable to that of normal individuals following the injection of a standard dose of epinephrine.

The question arose, too, as to whether the carbohydrate disturbances observed were not due primarily to removal of the adrenal medulla. This can be answered readily both from clinical and experimental observations. Patients with Addison's disease who have atrophy of the adrenal cortex, but with relatively intact medullae nevertheless display the same characteristic disturbances in carbohydrate metabolism as do those patients with extensive and universal destruction of the adrenals due to tuberculosis. Similarly Zwemer and his co-workers (51, 52) found that in demedullated cats no changes in the blood sugar level occurred as a result of the operative procedure. Boggild (53) observed similar results in dogs.

It is evident from these few casual observations that alterations in carbohydrate metabolism occur both in patients with Addison's disease and in most adrenalectomized animals. It is further evident that these disturbances are not related to destruction or removal of the medulla. Let us examine the available experimental data which would indicate that the adrenal cortex plays a fundamental rôle in the changes in carbohydrate metabolism.

Cori and Cori (54) showed that adrenalectomized rats, which had been fasted for 24 hours had practically no liver glycogen. Long, Katzin, and Fry (46) working with adrenalectomized rats and mice, found that so long as these animals are fed, normal levels of liver and muscle glycogen can be maintained, but when they are subjected to fasting a rapid depletion of liver glycogen ulti-

ately followed by a similar reduction in muscle glycogen occurs. The observation that fed adrenalectomized animals maintain normal stores of liver and muscle glycogen is contrary to the observations of Britton (55). This difference is probably due to the fact that the animals studied by Long and his group were maintained in normal electrolyte balance by the administration of sodium chloride. It is entirely conceivable that in the presence of uncontrolled disturbances in the electrolyte pattern there may also be an impairment in the ability on the part of the tissues to store glycogen.

Britton and Silvette (49) found that the low blood sugar and the depleted glycogen stores could be restored to normal by the administration of a potent cortical extract. They similarly observed, and this is of equal significance, that the administration of cortical extract was capable of increasing the blood sugar level and glycogen reserves of normal animals. These observations were confirmed by Thaddea (56) and to a considerable extent by Long, Katzin, and Fry (46). The latter authors differed with Britton and Silvette in that they observed no effect of the cortical extract on the level of the muscle glycogen, although the hepatic stores and the blood sugar level were considerably increased. Long and his group (46) further found that the administration of cortical extract could prevent glycogen depletion of the liver in fasting adrenalectomized rats and mice. If the observations of Long and his colleagues are correct, that the store of muscle glycogen is not affected by cortical extract, it is curious that an elevation in the blood sugar level and an increase in the liver glycogen should occur in the fasting animal. It obviously cannot be explained by a shift in the glycogen store from muscle to liver, since the former is not affected. It must, then, follow that the additional glycogen is obtained from some other source. The bulk of the evidence would indicate that this glycogen is obtained by the catabolism of proteins. Evans (57) has shown that fasting adrenalectomized rats excrete about 25 per cent less nitrogen than do normal rats under similar conditions. This observation was confirmed by Long and his group (46). In addition, they found that in both normal and adrenalectomized fasting rats and mice the administration of cortical extract was followed not only by an increase in liver glycogen and blood glucose, but that these were accompanied by a parallel increase in urinary nitrogen excretion. This would indicate that cortical extract intensifies the breakdown of protein with its conversion into glucose and accumulation of glycogen in the liver. Another approach to the same problem may be obtained by studying the effect of cortical extract on phlorhizin diabetes. Phlorhizin lowers the renal threshold for sugar, so that glucose is constantly being excreted in the urine as long as there are available exogenous and endogenous sources of sugar. Even in the fasting animals glucose continues to be excreted in the urine with the administration of phlorhizin. However, fasting adrenalectomized rats and dogs maintained in good health by the administration of sodium chloride, excrete much less sugar after administration of phlorhizin than do normal animals similarly treated (57). This defect is promptly corrected by treatment with whole adrenal cortical extract or certain crystalline fractions obtained from adrenal cortical extract

(58). These experiments would again suggest that adrenal cortical extract mobilizes the body protein, increases its catabolism and conversion to glucose.

Further evidence supporting the primary rôle that the adrenal cortex plays in carbohydrate metabolism is provided by studies of the depancreatized and partially depancreatized and adrenalectomized animal. Hartman and Brownell (59) and Long and Lukens (60) have shown that adrenalectomy modifies, in a favorable manner, the severe diabetes produced by pancreatectomy in the cat. Long and his coworkers (46) further found that a similar effect could be obtained in the partially depancreatized rat. When adrenal cortical extract was administered to these animals, the original severely diabetic state with marked glycosuria could be reproduced. These authors found, in addition, that cortical extract caused an increase in the urinary excretion of sugar in the partially depancreatized animal with intact adrenals. Sprague (61) confirmed these observations.

It is desirable at this point to summarize the various observations discussed. Adrenalectomized animals that are well fed and maintained on sodium salts have a fairly normal blood sugar level and normal glycogen stores in the liver and muscles. Starvation, however, causes a very rapid depletion of these stores and a drop in the blood sugar. The administration of a potent cortical extract, either to the fasting or fed adrenalectomized animal, results in a replenishing of the liver glycogen and an elevation in the blood sugar level, although it apparently exercises no effect on the muscle glycogen. The ability of cortical extract to increase liver glycogen in the fasting adrenalectomized animal without affecting the muscle glycogen would suggest that the added glycogen must come from some other endogenous source. The fact that there is an increased urinary excretion of nitrogen parallel to glycogen and glucose increase in the liver and blood, following treatment with extract, would suggest that the catabolism of protein, strongly influenced by adrenal extract, is the source of this endogenous glycogen. This is further borne out by studies on phlorhezin diabetes in the fasting adrenalectomized animals. The administration of cortical extract to these animals increases appreciably the urinary excretion of glucose. A further point in favor of the significant rôle that the adrenal cortex plays in carbohydrate metabolism can be obtained from studies conducted with depancreatized and partially depancreatized animals. Adrenalectomy in these animals modifies the severity of the diabetes, while the administration of cortical extract enhances it. Adrenal extract will cause an increase in the glycosuria in partially and totally depancreatized animals with intact adrenals. Finally, adrenalectomized animals are markedly sensitive to insulin (62), and are incapable of converting precursor substances like lactic or pyruvic acid into glycogen or glucose.

These observations would suggest that there is a very intimate relation between the adrenal cortex and carbohydrate metabolism. Disturbances in this latter function in adrenalectomized animals, and in patients with Addison's disease, cannot be explained simply on the basis of a non-specific phenomenon of the disease, but rather must be assumed to represent as primary, although

perhaps not as important, a defect as that of the electrolyte and water metabolism.

THE HORMONES OF THE ADRENAL CORTEX

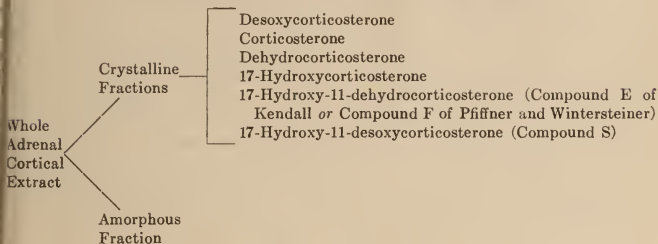
The attempt at substitutive therapy in the treatment of destructive diseases of the adrenals dates back to 1867 (63). In 1903 Adams (64) collected a total of 97 cases of Addison's disease from the literature, in which organo-therapy was employed in the form of desiccated whole adrenal and the desiccated extract and aqueous, alcoholic and glycerine extracts used either by mouth or by injections. Of this group of patients, 16 were reported as permanently improved. Among this group was a case reported by Osler (65) who responded particularly well to a glycerol extract of fresh sheep adrenal glands given both by mouth and by hypodermic injection. When the use of the extract was discontinued the patient was precipitated into acute adrenal insufficiency which terminated fatally.

These attempts at the manufacture of therapeutically efficacious cortical extracts were by far and large unsuccessful. The extracts were crude and of a very dubious and at best limited potency, and with the isolation of epinephrine further attempts at the isolation of cortical hormones were discontinued until the latter 1920s. In 1927, Rogoff and Stewart (66) succeeded in prolonging the survival period of adrenalectomized dogs with the use of saline extracts of whole adrenal glands. They called this extract "Interrenalin." In the same year, Hartman and his group (67) described an adrenal extract which prolonged the life of adrenalectomized cats. This extract, in contrast to that of Rogoff and Stewart, contained no adrenalin. In 1929, Pfiffner and Swingle (68) described the successful use of an alcoholic adrenal extract in adrenalectomized dogs. The use of these various extracts in the treatment of patients with Addison's disease and the brilliant results obtained stimulated interest both in the attempt to fractionate the adrenal cortical extract and to manufacture synthetic cortical hormones. Between 1936 and 1944, the important contributions to adrenal cortical organo-therapy consisted in the isolation of various crystalline fractions of the whole extract.

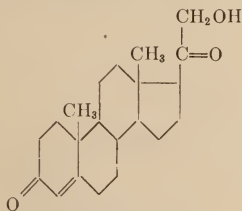
In 1936 and 1937, Mason, Myers, and Kendall (69) and de Fremery and his co-workers (70) isolated corticosterone and dehydrocorticosterone in crystalline form from the extracts of the adrenal cortex, and found that they could maintain adrenalectomized animals in good condition. A short while later, Steiger and Reichstein (71) announced the synthetic preparation of desoxycorticosterone acetate from Stigmasterol. Subsequently, Reichstein and von Eüw (72) succeeded in recovering this compound from an extract of the adrenal cortex. In 1940, Pfiffner and North (73) isolated 17- β -hydroxy-progesterone from the adrenal cortex. In addition, 17-hydroxy-11-dehydrocorticosterone, which is the so-called compound E of Kendall and compound F of Pfiffner and Winterstiner, and 17-hydroxy-11-desoxycorticosterone, or compound S (74), both hormones of important physiological significance, have been recovered from the adrenal cortex. Other fractions of dubious significance and doubtful structure have been isolated. After removal of the crystalline fractions from adrenal cortical extract, an amorphous residue of great physiological potency is left. The number of steroid hormones isolated from adrenal cortical extract total at

present 25 (75). Unquestionably, many more fractions will be extracted in the near future.

Active fractions isolated from whole adrenal cortical extract



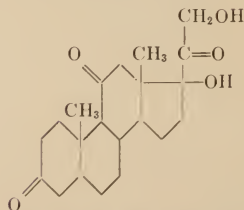
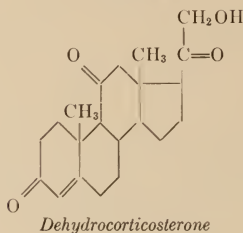
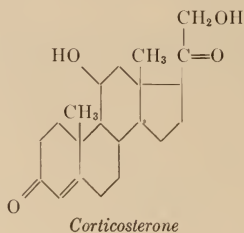
Of all the steroid hormones thus isolated, only those outlined in the preceding paragraph are known at present to have important physiological significance, and it is worthwhile to consider the nature of their activity:



Desoxycorticosterone

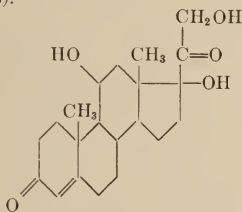
Causes a marked retention of sodium, chloride, and water, and increases the urinary excretion of potassium and phosphorus (72, 76). However, it exercises no effect on carbohydrate metabolism or the pigmentation of Addison's disease. In Addison's disease and in experimental adrenal insufficiency, it will restore the blood electrolyte pattern to normal, increase the circulating blood volume and elevate the blood pressure. The continued use of this hormone can result in edema and heart failure and in the temporary production of hypertension (77, 78, 79, 80). The hypertension thus induced bears no relationship to salt and water metabolism but is apparently a specific function of desoxycorticosterone. It is interesting that while whole adrenal cortical extract will elevate the reduced blood pressure of the patient or animal in acute adrenal insufficiency to normal levels it will not induce hypertension. Desoxycorticosterone, however, can cause the blood pressure to attain hypertensive levels but only in the presence of destroyed or extirpated adrenal cortices. It is difficult to induce hypertension in the normal individual or in the dog with intact adrenals with this hormone. These facts would suggest that desoxycorticosterone has a specific hypertensive effect which is apparently normally balanced by other fractions of the adrenal cortex.

It is interesting to observe that while this hormone has a pronounced salt retaining effect both in the presence of intact and destroyed adrenals, it cause an increase in the urinary excretion of sodium in the presence of hyperfunction of the adrenal cortex (81). Thus, in patients with Cushing's syndrome with adrenal virilism the administration of desoxycorticosterone followed by the intravenous injection of saline causes a considerable urinary outpouring of sodium in contrast to the behaviour of normal individuals similarly treated in which marked retention of the injected sodium is noted (81). There is no clear evidence to indicate the mechanism of this effect. It is possible that either the injected desoxycorticosterone in the presence of hyperfunction of the adrenal cortex is converted into a salt excreting hormone or stimulates the production of such a hormone. The former hypothesis is by no means far fetched since the conversion of one hormone into the other would at least seem theoretically feasible, in view of the close structural similarity between the two hormones.



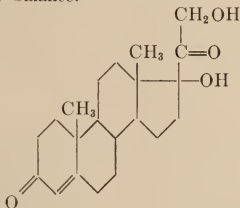
17-hydroxy-11-dehydrocorticosterone (Compound E of Kendall, and Compound F of Pfaffner and Wintersteiner)

These three compounds, in contrast to the action of desoxycorticosterone, exercise a marked effect on carbohydrate metabolism, and correct these defects in the adrenalectomized animals. Following injections of these hormones, glycogen is stored in the liver, the blood sugar levels are increased, and hypoglycemia is prevented. In addition, 17-hydroxy-11-dehydrocorticosterone, which has the most pronounced effect on carbohydrate metabolism, is also capable of restoring the ability of adrenalectomized rats to form glucose from lactic and pyruvic acids. However, corticosterone and dehydrocorticosterone exercise only a minimal effect on blood electrolyte metabolism with a slight retention of blood sodium (82), while 17-hydroxy-11-dehydrocorticosterone actually induces a negative sodium balance with a considerable increase in the urinary excretion of this ion (83).



17-hydroxycorticosterone

This compound exercises a marked effect on carbohydrate metabolism similar to that of corticosterone, dehydrocorticosterone, and 17-hydroxy-11-dehydrocorticosterone. However, in contrast to the first two hormones and to desoxycorticosterone, it causes an increase in the urinary excretion of sodium and induces a negative sodium balance.



17-hydroxy-11-desoxycorticosterone (Compound S)

This compound exercises no effect on carbohydrate metabolism (84, 85). The effect of this hormone on mineral metabolism has not as yet been adequately investigated.

When we examine the structural formulae of these various hormones, we find that those hormones with an oxygen atom at C11, such as corticosterone, dehydrocorticosterone, 17-hydroxy-11-dehydrocorticosterone, and 17-hydroxycorticosterone exercise a marked effect on carbohydrate metabolism (58). The presence of a 17-hydroxyl group, such as in 17-hydroxycorticosterone and

17-hydroxy-11-dehydrocorticosterone, causes the hormone to induce a negative sodium balance, in contrast to such hormones as desoxycorticosterone, corticosterone, and dehydrocorticosterone, which have no 17-hydroxyl group and which exercise a salt-retaining effect.

Whether a compound such as desoxycorticosterone can be converted in vivo into a salt excreting hormone like 17-hydroxycorticosterone is at present a moot point. The experiments sited previously in which desoxycorticosterone induces an increase in the urinary excretion of sodium in the presence of hyperfunction of the adrenal cortex would suggest that such a conversion could conceivably occur.

AMORPHOUS FRACTION

When the crystalline fractions are removed from whole adrenal cortical extract, a highly active residue is left. This amorphous fraction exercises no effect on carbohydrate metabolism, but is exceedingly potent in its effect on the distribution of electrolytes. According to Kendall (82) only one or two micrograms per kilogram of body weight is required to maintain a normal electrolyte pattern in adrenalectomized dogs. This is in striking contrast to the relatively large quantities of desoxycorticosterone required to produce the same effect. This contrast is particularly significant in view of the fact that desoxycorticosterone is the most potent crystalline fraction of adrenal cortical extract in its effect on electrolyte metabolism.

In the light of this review of the adrenal cortical hormones, it becomes evident that there is no one fraction which has all the functions of the adrenal cortex. In short, there is no one vital hormone of the adrenal cortex.

THE RELATION OF THE ADRENALS TO THE URINARY EXCRETION OF THE NEUTRAL 17-KETOSTEROIDS

The term 17-ketosteroid was applied by Callow and his coworkers (86) to those steroids with a ketone group on the 17th carbon atom and a free methylene group. These 17-ketosteroids which form the urinary products of androgenic metabolism arise from substances produced by the adrenal glands and male gonads (87-93). They are the neutral, non-phenolic fraction, and are divided into alpha and beta ketosteroids. The terms alpha and beta refer to the position of the 3-hydroxyl group. The alpha ketosteroids include androsterone and 3- α -hydroxyaetiocholanone-17, while the beta ketosteroids include dehydroisoandrosterone and isoandrosterone. The dehydroisoandrosterone and the isoandrosterone belong to the 3- α -hydroxysteroid series and are unsaturated. They can therefore be precipitated by digitonin, and thus separated from the alpha ketosteroids (94, 95). The neutral 17-ketosteroids normally present in male and female urines are androsterone, 3- α -hydroxyaetiocholanone, and dehydroisoandrosterone. Isoandrosterone is encountered in pathological urines (96) and perhaps in normal female urines (97). It is probable that the alpha neutral ketosteroids arise from both the adrenal and gonadal secretions, but available evidence indicates that the ketosteroids are excretion products of the cells of

the adrenal cortex only (88, 91, 93, 96, 98, 99). It should be emphasized that these neutral 17-ketosteroids are by no means the only ketosteroids of this character excreted in the urine, but rather represent those identified to date. Under normal circumstances, the alpha fraction constitutes the largest percentage of the total neutral ketosteroids excreted in the urine, while the beta fraction constitutes about 10–15 per cent of the total daily output (100). However, in the presence of adrenal cortical tumors, there occurs not only an increase in the total urinary excretion of the neutral 17-ketosteroids, but an increase in the percentage of the beta fraction. The increase in the beta fraction attains unusually high levels in the presence of adrenal cortical carcinomata (100). It is important to observe that androsterone has considerable androgenic activity. This is true, to a considerably lesser extent, of dehydroisoandrosterone, while 3- α -hydroxaetiocholanone-17 manifests no such activity.

The daily urinary excretion of total neutral 17-ketosteroids in normal individuals varies somewhat with the sex and considerably with the age of the individual. In general, males have a somewhat greater daily urinary excretion of these steroids than do females, and prior to sexual maturity the values for the total daily excretion are quite low. Thus Talbot and his group (100) find that the average daily excretion of total neutral ketosteroids of children under 7 years of age was 1.3 mgm. Between 7 and 12 years it was 4.0 mgm., and 8.2 mgm. between 12 and 15 years. Adult men excrete an average of 15.0 mgm., and adult women 10.2 mgm. The range in any one group is quite wide, as indicated by Talbot's table (100).

The daily excretion of neutral 17-ketosteroids is influenced by a variety of pathological states (101). Thus, it is low in malnutrition, anorexia nervosa, various gastrointestinal disturbances, anemia, infections, and in liver disease. It is extremely low, frequently reaching zero levels, in Addison's disease and in Simmond's cachexia. It is increased in adrenal cortical hyperfunction due to hyperplasia and tumors of the adrenal cortex and in Cushing's syndrome. The daily urinary excretion reaches particularly high levels, especially of the beta fraction, in carcinomata of the adrenal cortex.

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DIFFUSE GENUINE PHLEBECTASIA

MORLEY J. KERT, M.D. AND ARTHUR GRISHMAN, M.D.*

[From the Second Medical Service and the Department of Radiology]

Congenital dilatation of the veins of an extremity is a rare condition. In 1936 Freund (1) reported the first case in the American literature at the same time reviewing the 14 cases published up to that date. Only 3 more instances have been reported, one in the Turkish and two in the German literature (2, 3, 4). Most authors agree that the anomaly is most likely congenital in origin, an opinion which was stressed particularly by Freund. The following case is presented for its rarity, its association with other congenital anomalies, and because of the use of newer diagnostic procedures to confirm the clinical diagnosis.

CASE REPORT

History: (Adm. 500842) A woman, aged 22 years, was admitted to the hospital because of soft compressible lumps and dilated superficial veins over the external surface of the left leg present since the age of three years. At the age of nine she was knocked down by a motorcycle; otherwise the past history was completely negative. The left lower extremity had always been heavier than the right, the patient limping for as long as she could recall. When she was especially active the size of the left leg and thigh would increase; this was relieved by sitting down. Recently an elastic bandage on the left leg afforded more comfort.

During the past few years her visual acuity had been diminished at night. Her progress at school was unduly slow and she finally dropped out after reaching the seventh grade at the age of sixteen.

Examination: The patient was moderately well developed and well nourished. She had adenoid facies. Congenital bilateral partial cataracts were present. The lungs were clear. The heart was not enlarged and there was a faint systolic murmur at the apex. The blood pressure was 118 systolic and 66 diastolic in the arms, and 120 systolic and 80 diastolic in the legs. The skin was ichthyotic with a few pigmented areas.

The left lower extremity appeared larger than the right and there were soft bluish subcutaneous masses over the external surface of the left leg and lower thigh (fig. 1). The masses filled with dependency of the extremity and emptied with elevation. There were dilated veins over the dorsum of the left foot. The longitudinal arch of the left foot was poor and she walked with a valgus deformity. There were a few hard, almond-sized masses palpable in the left popliteal space, which gave the impression of calcifications. No bruit was audible over the left leg, and oscillometric readings in both lower limbs were equal and normal. The lower extremities were equal in length. Reflexes were physiological and sensation was normal.

Laboratory Data: Routine laboratory tests yielded normal findings. Electrocardiogram did not show any abnormalities. Circulation studies performed in the routine fashion were normal.

X-ray examination of the bones of the left lower limb revealed periosteal thickenings involving the outer aspect of the mid-third of the femur. There was some rarefaction of the medullary cavity of the lower end of the femur. Several calcifications were distributed throughout the leg and thigh (fig. 2).

* Fellow of the Dazian Foundation for Medical Research.

Course: Venography of the left lower extremity performed through injection of a vein in the lower lateral aspect of the leg revealed the superficial system in the lateral aspect of the extremity to be markedly dilated and tortuous. The deep system was not visualized (fig. 3).



FIG. 1

FIG. 1. Infra-red photograph of the external aspect of the left lower extremity. The extensive venous dilatations are clearly visible.



FIG. 2

FIG. 2. Roentgenogram of the left femur reveals periosteal thickening probably caused by the dilated deep veins of the thigh.

Arteriogram performed by injection into the left femoral artery showed the arterial system to be normal. The femoral artery and branches were somewhat smaller in calibre than the usual normal. Five seconds after the injection of the artery the popliteal vein became visible and appeared to be considerably dilated.

Venous pressure and pulse rate studies were performed to determine the effect of the pooled blood in the left lower extremity on the circulatory dynamics of the patient.

Venous Pressures

Recumbent.....	7.75 cm. of H ₂ O
Recumbent plus elevation of left leg.....	9.0
Recumbent plus elevation of right leg.....	7.75
Recumbent plus elevation of left leg immediately after standing for three minutes.....	10.5
Recumbent with both legs below heart level.....	3.5
Recumbent and then elevation of left leg.....	8.0 in $\frac{3}{4}$ min.
Recumbent plus elevation of right leg.....	8.5 (final reading)



FIG. 3. A. Venogram of the left lower extremity shows a marked dilatation and tortuosity of the superficial veins not having the corkscrew appearance of varicose veins.

B. The arteriogram of the left lower extremity is essentially normal.

C. Five seconds after the visualization of the arteries the dilated popliteal vein became visible. Laterally from the femur a diffusely dilated venous system is also visualized. Note the phleboliths.

Pulse Rate

Recumbent.....	76 per minute
Standing (immediately).....	100
Standing (after one minute).....	106
Standing (after five minutes).....	102
Left lower extremity elevated and tightly bandaged	
Recumbent.....	74
Standing.....	78
Standing (after five minutes).....	75

COMMENT

The clinical diagnosis of diffuse genuine phlebectasia has been fully discussed by Freund (1). Once one is acquainted with its existence the diagnosis is easily made. In the case presented the lesion was differentiated from varicose veins because of its existence from early childhood without previous local disease and because of the unilateral involvement. Furthermore, its anatomical appearance as seen venographically did not show the corkscrew configuration of varicose veins. Arteriovenous aneurysm was excluded because of the absence of arteriovenous communication in the arteriogram as well as of a bruit and characteristic hemodynamic changes.

The hemodynamic changes in our case were not different from those sometimes encountered in varicosities of the lower extremities. In both instances the assumption of the upright position caused pooling of venous blood and consequent diminished venous return to the heart. In patients with varicose veins Chapman (5) observed tachycardia and a drop of the blood pressure due to postural changes. In our case the pulse rate was accelerated 30 beats per minute after the patient assumed the upright position; no changes of blood pressure were noted. The postural tachycardia was eliminated by tightly bandaging the entire left lower extremity. A definite elevation of venous pressure was demonstrated by elevating the involved limb above heart level. This was most strikingly illustrated when an increase of venous engorgement was first produced by hanging the limb below body level.

Freund (1) has pointed out that the prognosis is poor because of the progressive nature of the lesion. The overlying skin may become atrophic and lead to bleeding and ulceration. Furthermore, one could postulate the ultimate development of symptoms due to the postural tachycardia. Chapman (5) in his cases described symptoms such as dizziness, headache, fatigue, etc., which he attributed to the altered hemodynamics in the upright position.

The therapy in this case will consist of elastic bandaging of the entire extremity. Its effectiveness seems suggested both by the subjective improvement and the elimination of postural tachycardia. Surgical intervention in these cases has not been permanently satisfactory. Radiotherapy as used by Freund in his case was also of no benefit.

SUMMARY

A case of diffuse genuine phlebectasia associated with congenital abnormalities and with postural tachycardia is presented. Venography and arteriography have been used to establish the diagnosis.

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RECURRENT GASTROJEJUNOCOLIC FISTULA

ERNEST L. SARASON, M.D.

[From the Surgical Service of Dr. John H. Garlock]

The development of a fistulous communication between the stomach, jejunum, and colon is perhaps the most serious complication of gastroenterostomy performed for duodenal ulcer. Gastrojejunocolic fistula is a result of the perforation of a gastrojejunal or marginal ulcer into the adjacent transverse colon. The purpose of this communication is to report the successful treatment of a recurrent gastrojejunocolic fistula, probably the first such case in surgical literature, and emphasize certain important surgical considerations involved in the treatment of this complication.

CASE REPORT

History: (Adm. 510011) The patient, a 58 year old physician, first entered The Mount Sinai Hospital in 1915 at which time he was suffering from a chronic duodenal ulcer associated with pyloric stenosis. A gastroenterostomy was performed and the patient was temporarily relieved of his main symptoms of vomiting and epigastric pain. Four years later he began to experience severe nausea and vomiting, and it soon became quite evident that the vomitus contained fecal material. There was no diarrhea. The patient was operated upon at the Mayo Clinic by the late Dr. E. Starr Judd, and there was demonstrated a gastrojejunocolic fistula. The operative procedure entailed the taking down of the gastroenterostomy, repair of the fistulous openings in the colon and jejunum and the performance of a new gastroenterostomy higher up on the posterior gastric wall. The post-operative convalescence was quite stormy and prolonged. The patient remained well until one year before the present admission to The Mount Sinai Hospital (August 31, 1943) when he noted intractable diarrhea. The patient complained of a fecal odor to his breath, but was free of abdominal pain. Since the onset of the diarrhea there had been a weight loss of 30 pounds.

Laboratory Data: Blood: hemoglobin, 83 per cent; white blood cells, 12,250, with 75 per cent polymorphonuclear leucocytes; urea nitrogen, 15 mg. per cent; chlorides, 595 mg. per cent; CO₂ combining power, 53 vol. per cent; total protein, 4.5 Gm. per cent; calcium, 11.2 mg. per cent; phosphorous, 4.8 mg. per cent; hematocrit, 43 per cent. Gastric analysis: no free hydrochloric acid and 10-20 units of total acid. Urine, negative. Electrocardiogram showed no abnormality.

Roentgenographic examination by barium enema (fig. 1) revealed a communication between the distal transverse colon and the stomach adjacent to the stoma of the gastroenterostomy. Barium meal examination disclosed dilatation of the jejunum adjacent to the stoma. At the two hour observation, a small amount of barium was seen in the splenic flexure of the colon which was confirmatory evidence of the existence of a jejunocolic fistula.

Course: The patient was given intravenous injections of 5 per cent glucose in normal saline, as well as a mixture of amino acids and vitamins in preparation for the first stage of the operation. Daily cleansing enemas were employed. Sulfanilamide was administered for forty-eight hours before and after each of the three operations.

First Operation. (9/8/43) (Dr. Garlock) This was a glass-rod colostomy of the hepatic flexure of the colon through a right subcostal incision.

The exteriorized loop of colon was opened with the cautery forty-eight hours later. Soon after, all movements by rectum ceased. Prior to the second operation the patient received many transfusions of whole blood and plasma. There was a considerable gain in weight and the patient presented a markedly improved appearance.

Second Operation: (9/29/43) (Dr. Garlock) Upper midline incision. There were extensive adhesions which rendered dissection difficult. An almost complete pyloric stenosis was found at the site of an old chronic duodenal ulcer. The duodenum was divided in its first portion and the stomach transected above the reentrant angle. The distal transverse colon was dissected away from the previous gastroenterostomy, leaving a one inch opening in the colon, which marked the site of the fistulous communication. This opening was closed in two layers. In freeing the jejunum from the stomach it was necessary to resect a two inch segment of jejunum, which contained a chronic peptic ulcer. An end-to-end jejuno-jejunostomy was performed. Following resection of the stomach a retrocolic gastro-jejunostomy was performed after the method of Hofmeister, distal to the jejuno jejunal



FIG. 1. Barium enema roentgenogram demonstrating fistulous communication between distal transverse colon and greater curvature of the stomach. Arrow indicates gastro-colic fistula.

anastomosis. Five grams of sulfanilamide powder were sprinkled into the peritoneal cavity and the subhepatic region was drained. During the operation a transfusion of 500 cc. of whole blood was administered. Plasma (500 cc.) was given immediately postoperatively.

The patient withstood the procedure very well and the postoperative course was quite uneventful. The operative wound healed by primary union.

Third Operation: (10/23/43) (Dr. Garlock) An extraperitoneal closure of the ascending colostomy was performed. Convalescence was smooth and the wound healed without infection.

The patient was discharged nine weeks after entry into the hospital. His general condition was improved and bowel habits were regular. All of the operative wounds were well

healed. When the patient was seen one month later he had gained 25 pounds in weight and was free of symptoms.

COMMENT

Reference to the literature (1) reveals that until a few years ago the surgical treatment of gastrojejunocolic fistula was attended by a mortality of 25 to 60 per cent. During the past few years there has been a marked improvement in the operative mortality because of a better understanding of the character of the disturbed physiology of the gastrointestinal tract and the necessity of staging the operative procedure. The recurrence of a gastrojejunal ulcer with subsequent gastrojejunocolic fistula formation in the case reported is a striking example of how the "ulcer diathesis" of the patient is in no way altered by a gastroenterostomy. Lust (2) reported the recurrence of a gastrojejunocolic fistula following simple closure of the perforated jejunal ulcer and the colonic fistulous opening without disconnection of the gastroenterostomy. It is important that a subtotal gastrectomy be performed at the time of the repair of the gastrojejunocolic fistula if recurrent jejunal ulceration with subsequent colonic perforation is to be avoided.

It is well known that a patient with a gastrojejunocolic fistula is a poor operative risk. The performance of the operation in stages has done much to reduce the operative mortality. Pfeiffer (3) proved by clinical and roentgenologic methods that the advanced malnutrition in these cases is not the result of a supposed short circuiting of food from the stomach into the colon, but rather the result of hyperperistalsis and impaired digestion consequent to the emptying of colonic contents into the upper intestinal tract. Pfeiffer deserves much credit for his recognition of the fact that this important physiologic disturbance can be corrected in large part by means of a proximal diverting colostomy. The subsidence of diarrhea following the performance of the ascending colostomy in the case reported illustrates the efficacy of this procedure. The preliminary colostomy offers three advantages: (a) it allows improvement in the nutrition of the patient, thereby enabling him to withstand the extensive procedure of repair of the fistula and subtotal gastrectomy; (b) by virtue of diversion of the fecal stream the inflammatory reaction in the tissues about the fistula will subside to a degree sufficient to render the second stage less difficult; (c) satisfactory healing of the repaired opening in the colon is much more likely if a proximal diverting colostomy is present. The liberal use of blood, plasma, and sulfonamides must not be overlooked in considering the factors responsible for the success and reduction of mortality rate attending this three stage operative procedure.

In the last 4 cases of gastrojejunocolic fistula operated upon by Dr. Garlock, it was noted that the proximity of the ascending colostomy at the time of the second stage rendered the gastric resection more difficult than under ordinary circumstances. For this reason, Dr. Garlock has modified the procedure and now performs a cecostomy through a right McBurney incision, delivering the cecum onto the abdominal wall. That complete fecal diversion does occur is

evidenced by the results in a recent case treated by this method. It is felt that this maneuver will greatly simplify the steps of the second operation, the really difficult one.

SUMMARY

1. The successful surgical treatment of a *recurrent* gastrojejunal colic fistula has been reported.
2. The rationale of the staged surgical procedure has been reviewed.

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MASSIVE PULMONARY EMBOLISM: IV¹

BASED IN PART ON A STUDY OF EIGHTY-EIGHT FATAL CASES²

HAROLD NEUHOF, M.D., AND SAMUEL H. KLEIN, MAJOR, M.C., A.U.S.³

ILLUSTRATIVE CASES

Case 1. Carcinoma of sigmoid colon. Biopsy of inguinal lymph node. Exploratory laparotomy; caecostomy. Death in 3½ hours on the 8th postoperative day.

History. W. H. (Adm. #362867) was a thin man, aged 70 years, who had abdominal pain for 3 years and increasing constipation for 2 months. A left inguinal lymph node was first excised to rule out regional lymph node metastasis. Exploratory laparotomy was performed several days later under spinal anaesthesia, supplemented by gas-oxygen-ether. An irremediable neoplasm was encountered, and a palliative caecostomy was made. The patient's condition after the operation was satisfactory for eight days, although his temperature for several days was about 101-102°F., and reached 101-103.4°F. during the 6th, 7th and 8th days. There was then a sudden change in his general condition; he complained of pain on both sides of the chest; his pulse became weak and rapid, the respirations shallow and edematous and he died 3½ hours after the acute onset.

Post mortem findings. The coronary vessels were patent. The right common iliac vein contained a substantial non-adherent thrombus. Blood streamed freely from both femoral veins. The pulmonary arteries throughout the right lung and the smaller branches in the left lung were filled with embolic masses (schematically represented in fig. 1). There were bronchopneumonic areas in both lower lobes.

Comment. Remarks in comment of this case will be found in comment on Case 55.

Case 55. Left ureteral calculi; prostatic hypertrophy; left meningioma (found at post mortem examination). Left uretero-lithotomy; suprapubic cystostomy. Postoperative course uneventful. Sudden circulatory collapse on the ninth day, with partial recovery. Death eleven days later.

History. M. B. (Adm. #388313) was an obese man, aged 63 years. Operation was performed under spinal anaesthesia. The postoperative course was entirely satisfactory for nine days. Suddenly he became cyanotic, cold and clammy; his breathing became rapid, labored and grunting in character; there was marked fall in blood pressure and he became unresponsive. The left arm felt colder than the right. The clinical impression was noted as "coronary artery closure with multiple emboli." He gradually improved following this episode. Electrocardiogram two days later was reported as indicating severe myocardial damage, although a definite diagnosis of coronary artery closure could not be made. The patient's general condition remained fair until the eighteenth day; he then became drowsy and subsequently stuporous. The blood urea nitrogen was only 39 mg. per 100 cc. He died two days later, eleven days after the episode of acute collapse.

¹ This is the fourth installment of a series of seven articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting the second in the Series of Monographs of The Mount Sinai Hospital Press.—Ed.

² From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital.

³ Major Klein, adjunct surgeon to The Mount Sinai Hospital and now serving overseas with The Mount Sinai Hospital Unit, has contributed the study of the fatal cases and the analysis on which the work is based.

Post mortem findings. In the larger branches of both the right and left pulmonary arteries there were cylindrical, purplish masses which were slightly adherent to the vessel walls. Many of the smaller branches were also occluded by mottled-gray and purple, friable, formed adherent masses (fig. 2). The left subclavian artery contained an adherent brown-purple friable thrombus which measured 2 x 0.5 cm.

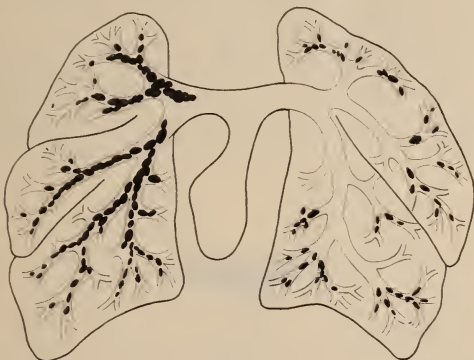


FIG. 1, CASE 1



FIG. 2, CASE 55

Comment. In both cases (Cases 1 and 55), the main pulmonary arteries were clear, but there was obstruction to the pulmonary circulation by emboli in the intrapulmonic branches of the pulmonary arteries. In the first case, death occurred $3\frac{1}{4}$ hours after embolization with the picture of cardiac failure and pulmonary edema. In the second case, the fatal episode lasted 11 days and

consisted of a combination of asphyxia, stupor (cerebral anoxemia?) and circulatory collapse. The adherence of the embolic masses to the walls of the pulmonary arteries signified their prolonged sojourn in these vessels.

Case 2. Uterine fibroids. Supravaginal hysterectomy, right salpingo-oophorectomy. Pulmonary signs and symptoms on the 2nd postoperative day, and again on the 6th and 7th days. Sudden death in 25 minutes on the 8th day.

History. E. E. (Adm. # 353365) was a well developed woman, aged 41 years. Operation was performed under gas-oxygen-ether anaesthesia. On the 2nd day, her temperature rose to 104°F., her respirations were 20-24 per minute; the breath sounds were suppressed and there was diminished resonance over the right base. These signs and symptoms were thought to be due to pulmonary atelectasis. She gradually improved in the next few days, but on the 6th and 7th days her temperature again rose to 103.8-104°F., the pulse was 138 and the respirations 32. She was moderately cyanotic. She again improved. On the 8th



FIG. 3, CASE 2

day, however, she suddenly called out and was found to be extremely pale. Her pulse was imperceptible. There was no cyanosis, dyspnea, or chest pain. She died 25 minutes later.

Post mortem findings. The wound and peritoneal cavity were clean. The coronary vessels were negative. There was an adherent grayish-red, firm, friable thrombus in the right internal iliac vein, the tail of which extended into the common iliac vein.

There were areas of bronchopneumonia in both lower lobes of the lungs, and the pleura was covered by thin fibrinous exudate. There was a small infarct in the lateral aspect of the right lower lobe, and another in its apical region.

The main pulmonary artery was empty, but the right and left main branches immediately beyond the bifurcation were completely occluded by large emboli (fig. 3).

Comment. The initial embolism and right lower lobe infarctions apparently occurred on the second postoperative day. The fever, tachycardia and cyanosis on the sixth and seventh days may be ascribed to the bronchopneumonia and pleurisy of the lower lobes. Death occurred after an acute episode lasting 25 minutes on the eighth day due to massive embolism of the right and left main pulmonary arteries. The clinical picture was essentially that of syncope.

Case 3. Acute appendicitis. Appendectomy. Postoperative course satisfactory. Pain in right calf on the 11th day, acute collapse 30 minutes later and death in 15-20 minutes.

History. J. R. (Adm. #387582) was a very obese woman, aged 55 years. Operation was performed under avertin, gas-oxygen-ether anaesthesia. At 4:00 a.m. on the 11th post-operative day, she awoke and complained of pain in the calf of the right leg. She had a bowel movement, and then 15 minutes later, vomited and moved her bowels again, this time involuntarily. She was also incontinent of urine. She complained that she felt weak, and she was cold and clammy, pulseless, and cyanotic, with circumoral pallor. She was very apprehensive and restless. Ten minutes later she was ashen gray; her breathing was labored and noisy. She apparently had no pain. She soon became suddenly rigid and died, about 15 minutes after the acute onset of collapse. The clinical diagnosis was "Pulmonary Embolism or Acute Coronary Closure."

Post mortem findings. The coronary vessels were negative. When the femoral vessels were cut across blood could be milked freely from the right femoral vein but none from the



FIG. 4, CASE 3

left. Almost completely occluding the mouth of the pulmonic valves and extending into the right ventricle from the pulmonary artery was a somewhat friable, roughly cylindrical, mottled red and gray thrombus with irregular rippling lines on its surface. The clot continued into the pulmonary artery, and at the bifurcation appeared to be doubled on itself. It then extended into and occluded both main pulmonary artery branches. The thrombus was nowhere adherent (fig. 4).

Comment. This case illustrates a rapidly fatal massive embolism, the clot extending from the right ventricle through the pulmonic valves into the main pulmonary artery and its two main branches. The fatal episode consisted of a combination of shock, asphyxia and syncope, accompanied by vomiting and sphincteric incontinence.

An interesting feature in this case was the occurrence of pain in the calf of the right leg only 15 minutes prior to the onset of the fatal episode, representing presumably the release of the embolus from the lower extremity.

Case 18. Cystocele and rectocele; uterine fibroids. Supravaginal hysterectomy, bilateral salpingo-oophorectomy, Polk operation, extraperitoneal ventrofixation of cervical stump. Convalescence uneventful until patient dropped over dead on the 11th postoperative day.

History. N. S. (Adm. #297654) was a very obese woman, aged 40 years, who was operated upon under gas-oxygen-ether anaesthesia for cystocele and rectocele and uterine fibroids. Preoperatively, slight pitting edema of both ankles had been noted. Her convalescence was entirely uneventful until the 11th day. Then, at 2:30 a.m., she was observed by the nurse to be sleeping quietly. Soon thereafter, she awakened and asked for a drink and for the bedpan. Two minutes later she gasped and dropped over dead.

Post mortem findings. The operative field was negative. The left lower lobe was collapsed.

There was a large grayish-red embolus in the right ventricle, almost completely filling the conus arteriosus and extending into the branches of the pulmonary artery for a short distance (fig. 5). The embolus in the right pulmonary artery was somewhat firmer and grayer than the one in the left.



FIG. 5, CASE 18

Comment. In view of the fact that death occurred instantaneously, this case may be an instance in which the mechanism of death was reflex cardiac or respiratory standstill, or both.

Case 4. Fracture of neck of femur. Reduction and insertion of Kirschner wires. Death in a few moments on the 14th postoperative day.

History. L. L. (Adm. #369178) was a frail and emaciated man, aged 80 years, who was admitted with a fracture of the neck of the left femur. Under avertin-gas-oxygen-ether anaesthesia, the fracture was manipulated and the fragments immobilized by Kirschner wires. Twelve days later, while psychotic, he jumped out of bed. X-ray examination revealed that the wires had become bent and displacement of the fracture fragments had re-occurred. Therefore, the following day the fracture was again manipulated, Kirschner wires inserted and a perforated Smith-Peterson nail threaded over one of the wires and hammered into place. The patient's condition was satisfactory following this procedure. While eating breakfast the following morning, he suddenly became cyanotic and death supervened in a few moments.

Post mortem findings. Wound clean. Fracture in good position. There was a massive recent thrombus in the main pulmonary artery which extended into the right and left main branches and tributaries (fig. 6). The thrombus was firm and well formed, but it was not adherent. The tail of the thrombus appeared fresher and darker than the rest and extended through the pulmonary conus into the right ventricle. About two inches beyond the origin of the right pulmonary artery, small firm clots were found in the primary branches of the right pulmonary artery.

Comment. This case is another example of massive pulmonary embolism producing complete obstruction and very rapid death. The only clinical sign noted in this patient was cyanosis (asphyxia).

Cases 2, 3, 4, and 18 have been selected to illustrate massive pulmonary embolism producing rapid death. In each of them, however, the fatal episode presented a different clinical picture. It should be noted that none of these patients had chest pain.



FIG. 6, CASE 4

Case 10. Carcinoma of the rectum; uterine fibroids. Rectal biopsy. Collapse two days later; death in 7½ hours.

History. D. S. (Adm. #333282) was a well-developed woman, aged 57 years. She complained of anorexia of six months' duration and a tender abdominal swelling for six weeks. Six months prior to admission she had noted swelling of the veins of her left leg. Examination revealed that she had lost some weight. There was a large pelvic mass, and also a mass on the posterior rectal wall, fixed to the sacrum. Proctoscopy was performed and a biopsy taken of the rectal lesion, which was reported adenocarcinoma.

Two days later, she awoke from sleep and stated that she felt she was dying. She complained of precordial pain. Her skin was cold and clammy, her lips were dry, and the pulse was regular but of poor quality. The blood pressure was 90 systolic and 40 diastolic, the respirations were 46 per minute. The heart according to physical signs, was displaced to the left, and pure bronchial breathing was heard over the medial part of the right chest anteriorly. The clinical impression was that the patient was suffering from an acute coronary occlusion. She was placed into an oxygen tent. Four hours later she was still cyanotic, and complained of pain in the left arm and in the precordial area. The blood count was 26,500 white blood cells, 74 per cent polynuclear leucocytes, 25 per cent lymphocytes and 1 per cent monocytes.

The electrocardiogram showed T3 slightly inverted and cove-shaped; T1 and T2 upright and cove-shaped. She was dead 7½ hours after the onset of the acute episode.

Post mortem examination. There were numerous moderate-sized varices over the anterior and lateral aspects of the lower portions of both legs, and marked venous dilatation over the anterior tibial aspects of both legs. The veins of the legs were not dissected. The peritoneal cavity was clean. There was a 1½ cm. grayish-white soft mass attached loosely to the intima of the inferior vena cava just below the point where the hepatic vein entered. This mass could be moved freely in the lumen of the vena cava.

Several arteries scattered over the cut surfaces of both lungs contained non-adherent embolic material. There was a cylindrical reddish-black embolus lying free in the outflow tract of the right ventricle, extending into the pulmonary conus and above the pulmonary valves. There was a break at this level and the embolus then extended into both the right and left pulmonary arteries (fig. 7). The coronary arteries were patent.



FIG. 7, CASE 10

Comment. This case illustrates the clinical picture, including the typical electrocardiographic changes, of acute coronary artery occlusion produced by a massive embolus which involved the outflow tract of the right ventricle, pulmonary conus and valves, and the right and left main pulmonary arteries. The coronary arteries were all patent. Despite the great degree and extent of the pulmonary embolus, the duration of the fatal episode was 7½ hours.

Case 5. Seminoma of the testis. Orchidectomy. Signs of pneumonia on the 9th day, which cleared up. Sudden collapse and death in a few hours on the 36th day.

History. L. B. (Adm. #303391) was a somewhat overweight man aged 45 years. He had swelling and induration of the right testicle for about a year. Under gas-oxygen-ether anaesthesia, orchidectomy was performed for seminoma. Nine days later he complained of severe pain in the right lower chest on breathing. There were dullness and râles over the right lower lobe posteriorly. His temperature was 101-103.6°F. X-ray examination of the chest revealed infiltrations in both lower lobes which were diagnosed as bronchopneumonia. Five days later the pain in the chest had disappeared, but there were still dullness and bronchial breathing over the right lower lobe. The temperature gradually fell to normal, the pulmonary signs cleared and the patient was discharged from the hospital on the 20th postoperative day.

On the 36th day, he suddenly became weak and dyspneic. He was brought to the hospital a very short time later. He was in collapse, was dyspneic, orthopneic, cyanotic. The pulse was rapid and thready, and the heart sounds were of the "gallop rhythm" type. The temperature was 104°F., the blood pressure was 80 systolic and 60 diastolic. There were physical signs of right lower lobe consolidation. The clinical picture was that of myocardial failure and shock. The patient died 6 hours after admission.

Post mortem findings. There were 2 pulmonary infarcts, one in the right middle lobe at its base, and the other on the diaphragmatic surface of the right lower lobe. There were adherent, pea-sized, reddish, irregular thrombi throughout the course of the spermatic vein on the operated side. The prostatic venous plexus was congested. In 2 veins of 5-6 mm. caliber, there were long tubular adherent grayish red thrombi, with a small amount of propagated clot in the direction of venous drainage.

Just at the bifurcation of the pulmonary artery there were present in both the right and left branches, two large, red, slightly adherent emboli with considerable propagated clot extending into the smaller branches of the right pulmonary artery (fig. 8). In the areas of infarction all the branches were filled with tubular adherent red thrombi.

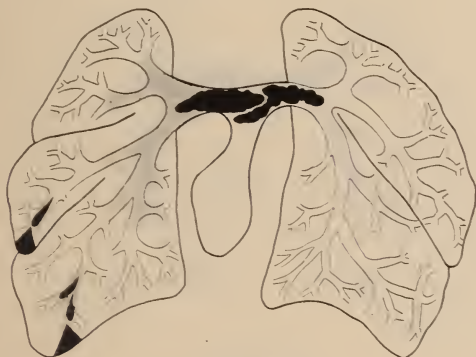


FIG. 8. CASE 5

Comment. The thoracic pain, fever, physical and roentgen signs of "pneumonia" of the right lower lobe were due to minor embolism and infarction occurring on the ninth postoperative day.

The massive fatal embolism of the right and left main pulmonary arteries occurred unusually late in the postoperative period (36th day). The fatal episode lasted more than six hours, during which time the embolus had already begun to become adherent to the intima of the vessels. There was also considerable propagation of clot into the smaller branches of the right pulmonary artery. The clinical picture of the fatal episode was that of myocardial failure and shock.

Case 6. Chronic glomerulonephritis, nephrotic phase; generalized anasarca. Progressively downhill clinical course following a fainting spell. Death 6½ days after the syncopal attack.

History. I. K. (Adm. #342741) was a well-developed and well-nourished woman aged 48 years. She had had scarlet fever at the age of 16 years, and post-partum pyelitis at the

age of 36. About 9 months before admission to the hospital she began to have progressively increasing edema. She presented the clinical picture of nephrosis, which was considered in this case to be a phase of chronic glomerulonephritis.

She was treated with thyroid extract, high protein diet, and diuretics. Despite some loss of weight under this regime, there was no appreciable diminution in the anasarca.

About a month after admission, she experienced a spell of weakness and she fainted. Following this episode she went progressively downhill and died $6\frac{1}{2}$ days later. During this interval, the only signs were marked asthenia and dyspnea. Nevertheless, the clinical impression, as noted on the chart, was that of pulmonary embolism or acute coronary artery closure.

Post mortem findings. Both renal veins contained large partially adherent and organized thrombi, almost completely occluding the lumen and extending out to the junction with the vena cava and into the substance of the kidney. The renal arteries were negative.

The ovarian vein on the left side contained a partially adherent organized thrombus, partially occluding the lumen.



FIG. 9, CASE 6

The main branches of the pulmonary artery on both sides and the smaller ramifications were all almost completely filled by partially adherent and organizing emboli with thin reddish propagated ends (fig. 9). There were many partially occluded blood vessels in both lungs and several small infarcts associated with thrombosed vessels in both lung bases.

The coronary vessels were patent.

Comment. Correlating the pathological findings in the lungs with the clinical picture, one may invoke two possible mechanisms to explain the fatal episode in this case: (1) the initial syncopal attack may be ascribed to peripheral emboli causing the infarctions in the bases of both lower lobes. The massive clots found in the main pulmonary artery branches and their ramifications may have resulted from centrifugal propagation of thrombosis from the original peripheral emboli, or from local accretion and propagation of clot upon secondary emboli during the terminal $6\frac{1}{2}$ days of life. Either or both processes produced obstruction of the pulmonary circulation and death. (2) The syncopal episode which initiated the terminal episode may have been due to multiple diffuse

embolizations, which the patient survived because of only partial obstruction of the pulmonary arterial circulation. Death occurred $6\frac{1}{2}$ days later when the obstruction became complete by gradual, progressive accretion and propagation of clot upon the original emboli.

Case 11. Choledocholithiasis. Jaundice. Choledocholithotomy and drainage of the common duct. Collapse on the 6th postoperative day, with prompt recovery. Sudden collapse and death in 10 minutes 5 days later.

History. R. G. (Adm. # 331986) was an obese woman, aged 52 years, who came to the hospital with a 6 weeks' history of epigastric pain and icterus. She had had attacks of right upper quadrant pain for 19 years. On examination, the patient was jaundiced; the urine contained bile but the stools contained bile pigment. The diagnosis was incomplete biliary obstruction. She was operated upon under spinal anaesthesia, supplemented by gas-oxygen-ether. The common duct was distended and contained many calculi. These were removed and the common duct drained. The gall bladder was not removed.



FIG. 10, CASE 11

The postoperative course was uneventful until the 6th day, when the patient suddenly became dyspneic and cyanotic; her skin was cold and clammy and her pulse was weak and rapid. The symptoms and signs of collapse cleared up rapidly following the hypodermic administration of morphine. It was the clinical impression that she had suffered a pulmonary embolism. The patient was again well until the 11th day, when she suddenly became markedly dyspneic and the nurse found her gasping. Her skin was cold and clammy and she was extremely cyanotic. The respirations were 48 per minute and the pulse rate 146. In a few minutes she no longer responded, the cyanosis was extreme and she died 10 minutes after the acute onset of collapse. The clinical diagnosis was pulmonary embolism, but the possibility of acute coronary occlusion was also entertained.

Post mortem examination. Slight varicosities of the lower extremities were noted. The veins were not dissected. The coronary vessels were normal. There were no pulmonary infarcts.

The right pulmonary artery was filled with a coiled, firm thrombus which was slightly adherent to the vessel wall and extended for a short distance into the left pulmonary artery. The clot had a fairly uniform diameter of about one-half inch. Lying free in the right ventricle was a coiled, firm thrombus about 15 cm. long, situated mainly in the outflow tract but not entering the pulmonary artery (fig. 10).

Comment. This case offers incontrovertible proof that a patient can survive a massive pulmonary embolism. The adherent massive clot found at autopsy in the right and left pulmonary arteries was undoubtedly the cause of the acute collapse, dyspnea and cyanosis on the 6th postoperative day. Death, which occurred 10 minutes after the sudden onset of asphyxia, shock and coma 5 days later, was due to a second large embolus which lodged in the right ventricle.

Case 12. Incisional ventral hernia. Hernioplasty. Pain in left chest and friction rub on 4th postoperative day. Acute dyspnea, cyanosis and shock on 10th day. Death 2 days later.

History. T. S. (Adm. #331170) was an obese woman, aged 71 years, who was operated upon under spinal anaesthesia for the repair of an incisional ventral hernia. Her post-operative course was uneventful until the 4th day when she suddenly developed sharp pain in the left lower chest. A leathery friction rub was heard in this area on the following day. Her condition was good. Six days later she awoke suddenly from sleep, screamed and cried



FIG. 11, CASE 12

out that she was dying. She was markedly dyspneic and cyanotic, and her pulse was weak and rapid. The heart sounds were normal. Moist râles and a leathery friction rub were heard in the left axillary line between the 8th and 11th ribs. Her temperature was 97°F. The patient's condition was improved by the administration of oxygen, morphine and caffeine. She was mentally clear, but apprehensive. On the following day, the temperature was 101.8°F., blood pressure 110 systolic and 70 diastolic. Blood count: white blood cells, 15,700; 86 per cent polynuclear leucocytes, 14 per cent lymphocytes. The electrocardiogram did not suggest coronary occlusion. Late that night the patient became irrational; her respirations were labored but not rapid. She vomited several times. Next day, her temperature rose to 104.4°F. She went into shock, from which she did not recover. Clinical impression: Pulmonary embolism, the previous pulmonary signs probably being due to infarction. Death on the 12th postoperative day.

Post mortem examination. There were no pulmonary infarctions, and no pleurisy. The lungs were congested. There was a large Y-shaped thrombus filling the main pulmonary artery and both branches (fig. 11). The lower end of the thrombus was lightly attached to the anterior wall of the right ventricle. The greater part of this thrombus was fresh, soft and friable, but at the bifurcation there was an older firmer core which ran transversely

from the right to the left lung thus forming a definite "riding" embolus. It was not adherent, but continued as a thrombus into the smaller branches on both sides.

Long well-formed non-adherent fresh thrombi were found in both external iliac veins.

Comment. This case also illustrates initial survival following a massive pulmonary embolism of the right and left main pulmonary arteries, with death ensuing two days later.

Reconstructing the clinical course of events from the pathological findings, incomplete nonfatal embolic occlusion of the right and left main pulmonary arteries was transformed into complete fatal obstruction of these vessels as well as the main pulmonary artery, by local accretion of clot upon the original embolus.

(To be continued)

ESSAYS ON THE BIOLOGY OF DISEASE¹

ELI MOSCHCOWITZ, M.D.

CHAPTER 7

THE BIOLOGY OF FOLLICULAR LYMPHOBLASTOMA

In 1925, Brill, Baehr and Rosenthal (1) described a disease with clinical and morphological characters that warranted a separate classification in the broad group of lymphomata. In a number of papers since then Baehr and his associates have amplified this concept and, what is of special significance, have observed a sufficiently large series of cases of follicular Lymphoblastoma to enable them to study their end results.

For the following exposition of the clinical and morphological characteristics of the disease, I am indebted to the latest publication of Baehr and Klemperer (2).

In the earliest stages, the disease is asymptomatic except for a generalized painless enlargement of the lymph nodes and usually but not always of the spleen. The blood count is normal and it is difficult to differentiate the condition of a simple hyperplasia. The enlargement of the lymph nodes is due to enormous enlargement of the lymph follicles which compress the intervening lymph sinuses. The follicles appear like huge germinal centers. Under higher magnification the cells are typical lymphoblasts. The capsules of the gland show a tendency to invasion, which becomes permanent in the later stages. The spleen when enlarged may reach enormous dimensions. Microscopically, it is thickly studded with large Malpighian bodies of similar morphology to those in the lymph nodes. Their enormous number proves that they do not represent hyperplasia but a new formation of giant follicle-like structures. The process may involve tissues that contain but small quantities of lymphoid tissues, for instance, the orbit (leading to proptosis), the breast, the lachrymal glands, the subcutaneous fat, etc. Strangely enough, the tonsil and the lymphoid tissues of the gastrointestinal tract are never affected. Serous and chylous effusions in the pleura and peritoneum are common and are due to compression of the lymph sinuses interfering with the flow of lymph.

The disease usually presents a milder course than the conventional lymphosarcoma and is particularly radiosensitive so that both glands and spleen may melt away after only a few applications of the Roentgen rays. Unfortunately, the disease does not remain cured; in the majority of cases, the disease returns,

¹ This is the seventh chapter in a series of essays by Dr. Eli Moschcowitz, in which an attempt will be made to interpret certain forms of chronic disease from the biologic viewpoint, as opposed to the current trend toward rigid classifications implying a concept of disease as a more or less static phenomenon.

According to present plans, these essays will appear in consecutive issues of the *Journal of The Mount Sinai Hospital*. When the publication of the projected series of essays is completed, the several installments will be assembled and printed as a monograph.—Ed.

sometimes after many years (4 to 15 years), the glands become Roentgen resistant and the patient succumbs. The morphology of the glands now bears every resemblance to those usually seen in the ordinary type of lymphosarcoma. Symmers (3) and Sugarbaker and Craven (4) reported a number of similar transformations. In 1932, Baehr reported that 8 out of 19 patients died and 8 of those who could be followed were still alive at the end of between one and fourteen years.

Another eventuality of follicular lymphoblastoma is chronic lymphatic leukemia. Baehr and Klemperer (2) saw two cases, Symmers (3) four and Gall, Morrison and Scott (4) one case.

It is very evident therefore that follicular lymphoblastoma is in most instances, the forerunner of lymphosarcoma and less frequently of lymphatic leukemia.

The Biology of Follicular Lymphoblastoma



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LIFE'S LATER YEARS

STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[*New York City*]

PART 5¹

ROMAN ATTITUDES AND OPINIONS

"When Greece was at its height Rome was the land of the soldier, the peasant, and the small trader; a people without art, without literature, and without philosophy" (1). The force of this statement is enhanced by the realization that southern Italy was an important part of Magna Graecia and shared actively in all the manifestations of Greek culture. The resistance of the Roman to the infiltration and the absorption of new ideas was one of his outstanding qualities. Pliny the Elder points out that for 600 years Rome existed without doctors. In 146 B.C. after the fall of Corinth, Greek physicians established themselves in Rome and later achieved recognition through the professional success of Asclepiades of Bythynia (124 B.C.). He is notable to us as a pioneer in the humane treatment of mental diseases, allowing the patients to enjoy daylight, employing occupational therapy, and using wine and music as sedatives.

Of the numerous individual practitioners whose names have come down to us, only a few stand out above all the rest. Celsus, who flourished in the first century A.D., is one of the great medical amateurs. He wrote the famous *De Re Medicina*, entirely neglected in his own day, but greatly celebrated during the Renaissance, not only for its medical content but also for its linguistic and rhetorical excellence. The comments on old age and its diseases are almost altogether repetitions of Hippocratic observations. Dioscorides, living in the second half of the first century was, according to Garrison, the originator of materia medica, the first to write on medical botany as an applied science. Aretaeus the Cappadocian, in the second century A.D., is notable for his exact descriptions of disease in the Hippocratic style, and particularly for his full differentiation of the types of mental disease, contrasting the variability of manic-depressive mental states with the fixed unchanging picture of senile melancholia.

The greatest physician of this period was Galen (131-201 A.D.) whose versatility and varied talents combined with untiring energy produced a whole library of publications on all phases of medicine. He made real contributions to anatomy, physiology and pathology; he was actually the first to introduce the experimental method in medicine. Galen nevertheless was essentially a philosophical theorist with an explanation for everything in a highly dogmatic manner. The resulting effect on medical progress is incalculable. "After his death

¹ This is the fifth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting the third in the Series of Monographs of The Mount Sinai Hospital Press.—Ed.



FIG. 1



FIG. 2

FIGS. 1 AND 2. Marble portraits of elderly women from the period of the Roman Empire. No attempt has been made to flatter the subject.
(Reproduced by permission from "Art Without Epoch," by L. Goldscheider, New York, Oxford University Press, 1937).

European medicine remained at a dead level for nearly 14 centuries" (Garrison). He was regarded as the court of last resort in all medical disputes and his assumption of infallibility was particularly acceptable to those who cherished every regard for his authority. Galen's complicated explanation of physiology was based on the qualities (hot, cold, moist, dry) and the humors (blood, phlegm, yellow bile, black bile). He describes four ages, youth (hot and moist), manhood (hot and dry), age (cold and dry), senility (cold and moist) (2). This interpretation of human physiology will recur again and again, as we trace our theme through succeeding centuries.

In "*De sanitatem tuendam*" Galen discusses the hygiene of old age in great detail, emphasizing exercise, diet, the care of the bowels, sleep, and the use of wine. Although it is the style to belittle this great physician because his teachings became medical dogma for so many centuries, it must be admitted that the problems of caring for the aged are analysed with rare good sense. In emphasizing that an old man's experience must determine whether a milk diet be proper for him or not, Galen says, "I knew a husbandman above an hundred years old, whose principal food was goat's milk, with which he mixed sometimes bread and sometimes honey; and now and then he ate it boiled with tops of thyme. A neighbor of his imagining that milk was the cause of the old man's long life, would try it in imitation of him, but could never bear it in any form, for it lay heavy on his stomach, and soon raised a swelling in his left side. Another making the same experiment, found milk agreed with him perfectly well, till after the seventh day of trial, when he felt a hard tumor in his right side which occasioned a tension with spasms quite up to his throat. I have also known some, who, from long use of milk, had contracted a stone in the kidneys, and some who lost their teeth; while others have lived upon it many years in health" (3).

Garrison (4) points out how rich as medical sources are the Roman secular writers, the poets, dramatists and essayists. Here we also find important observations bearing on the political and social status of the aged, pictures of their peculiarities and moralising on their sad fate. In Terence's *Phormio* (Act 4, Scene 1) we find the famous line, "*Senectus ipsa est morbus*," "Old age is itself a disease," which epitomizes the attitude of the physician from ancient times down almost to our own day. Even now we have difficulty in differentiating between the diseases that occur in the aged, and the involutionary changes that occur with age in all living matter. Cicero, Horace and Seneca made contributions of this kind that in the succeeding centuries were repeated over and over again, often in modified forms which, passed off as original, are still recognizable.

In his "Cato the Elder on Old Age," (5) Cicero (106-43 B.C.) places in the mouth of the aged Cato the exposition of a point of view of an old age which may be considered as representative of the opinion of aging Romans. While it leans heavily on Plato's "Republic," Chapters 2 and 3, as well as on Xenophon's *Oeconomicus* and *Cyropaedia*, it is distinctive as an attempt to define the values of old age and is unique in its optimistic tone. These qualities have insured its immortality. As recently as 1867, Charcot (6), the eminent French clinician, could say without exaggeration, "Most of the medical works of the past century which touch, in a special manner, upon the senile period of life, have a literary or

philosophical bearing; they are more or less ingenious paraphrases of the famous treatise *De Senectute* of the Roman Orator." In the introduction dedicating the work to his friend, Titus Pomponius Atticus (then 65 years old), Cicero (then 62) explains that his purpose has been to "lighten both for you and for me our common burden of old age; which, if not already pressing hard upon us, is surely coming on apace." The writer's views are brought out in the following excerpts from the essay.

"It is their own vices and their own faults that fools charge to old age."

"It is not by miracles, speed, or physical dexterity that great things are achieved, but by reflection, force of character, and judgement; in these qualities old age is usually not only not poorer, but is even richer."

"Rashness is the product of the budding-time of youth, prudence of the harvest-time of age."

"The aged remember everything that interests them."

"...Solon, whom we see boasting in his verses that he grows old learning something every day. And I have done the same, for in my old age, I have learned Greek, which I seized upon as eagerly as I had been desirous of satisfying a long continued thirst, with the result that I have acquired first-hand the information which you see me using in this discussion by way of illustration."

"An intemperate youth delivers to old age a body all worn out."

"But it is our duty, my young friends, to resist old age; to compensate for its defects by a watchful care; to fight against it as we would fight against disease; to adopt a regimen of health; to practice moderate exercise and to take just enough food and drink to restore our strength and not to overburden it. Nor, indeed, are we to give our attention solely to the body; much greater care is due to the mind and soul; for they, too, like lamps, grow dim with time, unless we keep them supplied with oil. Moreover exercise causes the body to become heavy with fatigue, but intellectual activity gives buoyancy to the mind."

"... if reason and wisdom did not enable us to reject pleasure, we should be very grateful to old age for taking away the desire to do what we ought not to do. For casual pleasure hinders deliberation, is at war with reason, blindfolds the eyes of the mind, so to speak, and has no fellowship with virtue."

"Bear well in mind that in this entire discussion I am praising that old age which has its foundation well laid in youth. Hence it follows—as I once said with the approval of all who heard it that old age is wretched which needs to defend itself with words. Nor can wrinkles and gray hair suddenly seize upon influence; but when the preceding part of life has been notably spent, old age gathers the fruits of influence at the last."

"But, the critics say, old men are morose, troubled, fretful and hard to please; and, if we inquire we shall find that some of them are misers, too. However, these are faults of character, not of age."

Cicero closes with a philosophic discussion of death, expressing his belief in the immortality of the soul. "And, if I err in my belief that the souls of men are immortal, I gladly err, nor do I wish this ever, which gives me pleasure, to be wrested from me while I live." In this essay we have old age defended, it is true by a man of means, position and intellectual resource, and yet portrayed with great insight and real understanding in such a way as to convey a message that after many centuries brings real cheer to many an old man (7). Among the writers of antiquity, in fact of all time, no one has more effectively and earnestly endeavored to bring forward the positive side of the picture of old age.

In his *Ars Poetica*, Horace (65-8 B.C.), (well known to high school and college students of the last generation, and far more highly regarded by them than the author of *In Catilinam*), attempts to instruct an aspirant in the technique of writing. In the course of this poetic discourse he describes the various kinds of characters which one must put into a play or a story. His description of old age, complete in a few lines, is so vivid, so realistic, so searching, that it ranks as one of the great classical treatments of the subject and has had the most widespread and varied influence throughout succeeding generations.

*"Grey hairs have many evils; without end
The old man gathers what he dare not spend,
While, as for action, do what he will,
'Tis all half-hearted, spiritless, and chill;
Inert, irresolute, his neck he cranes
Into the future, grumbles and complains,
Extols his own young years with peevish praise,
But rates and censures these degenerate days" (8).*

These lines of Horace have been traced by G. R. Coffman in a charming and scholarly essay (9), from their appearance in the time of Augustus to their reappearance in Chaucer's "Canterbury Tales" where they form part of the Prologue to the Reeve's Tale. In following the adventures of these verses over a period of 13 centuries one encounters many little known social and religious associations. Some of these throw light on the medical history of old age and will be quoted in due course and with grateful acknowledgement of Professor Coffman's erudition. The sources of Horace's inspiration are to be found in Aristotle rather than Plato, as the passages quoted in the previous sections will amply testify. The reader of Horace's poetry will find many other allusions to old age and its woes. The realism is bitter, almost savagely brutal, especially as regards women. One recalls particularly such poems as "The Shortness of Life" (*Eheu fugaces*), "Vanity of Riches" (*non ehur neque aureum*), "Be your age, Chloris" (*uxor pauperis Ibyci*) and "Too Old for Love" (*intermissia, Venus, div*).

Seneca (c. 3 B.C.—A.D. 65) was famed as a philosopher, dramatist and statesman. Of his many works, the best (so thought Montaigne) is his "Letters to Lucullus," which are not really letters but collections of maxims and moral remarks, representative of the Stoic philosophy of which he was a leading exponent.

"Of what use to such a man are 80 years spent in doing nothing? It is not in having lived; he has merely passed through life. It is not in dying late; he has been dead very long. It is by actions and not by its duration that life must be measured. He has lived for 80 years; say rather that he has existed for 80 years so long as you understand by that he has lived as we say the tree lives."

"... It is in mankind to preserve old age with care—that age whose fruit is more abundant, and the guardianship less irksome—that age which makes a more vigorous use of life when it knows that it is agreeable, useful and desirable to someone in the household. Besides this care is accompanied by joy in the house which is its reward. What is sweeter than to be sufficiently dear to a wife as to become dearer to yourself thereby?"

"We make the mistake in common of only believing in the approach of death in old age and in our declining years, while childhood, youth and other periods of life are leading up to the same end. Infancy is swallowed up by childhood, childhood by the age of puberty, the age of puberty by youth, youth by old age. Consider well, and you will find that our growing powers are but a series of losses."

"Let us try to make our life like to precious metals which have much weight in little compass; it is by our actions and not by length of life that we measure it. It is possible and even common to have lived little although long."

This discussion of the Roman lay contributors to our narrative serves to reinforce that feeling of nearness to ancient Rome, to which Sir Clifford Allbutt has called attention, pointing out that it seems no further off than the time of Queen Anne, and indicating how much more alien to us is the Middle Age with its many strange customs and viewpoints.

The centuries that followed the Golden Age of Augustus were marked throughout the Roman world by the steady deterioration of science in general and medicine in particular. The fine free spirit of the classical Greek tradition was hopelessly corrupted by the mingling of the old Roman superstitions with cults from Phrygia, Egypt, Persia and Syria, all glorifying the supernatural and the mystical and led to an increasing respect for Oriental magic and occultism. The physician, according to Garrison, became more and more a mercenary parasite and vendor of quack medicines. Oribasius (325–403 A.D.), Aetius (sixth century A.D.), Alexander of Tralles (525–605 A.D.), Paul of Aegina (625–690 A.D.) comprise the notables of these latter days, whose chief interest lies in their having

based much of their writings on the works of other men which would otherwise have been lost forever. In originality of thought or observation their efforts are largely lacking. An outstanding effect of Christian teaching with its emphasis on aid to the poor, the helpless and the sick, was the establishment of hospitals. This movement had its start following closure of the Asclepieia and other pagan temples by Constantine in A.D. 335. Gradually (10) these institutions became specialized and were differentiated according to their purposes: "Nosocomia or claustral hospitals, for the reception and care of the sick alone; Brephotrophia, for foundlings; Orphanotrophia, for orphans; Ptochia, for the helpless poor; Gerontochia, for the aged; and Xenodochia, for the poor and infirm pilgrims." At this early date between the fourth and sixth centuries were laid the patterns of public and private philanthropy which are familiar in our own communities.

To regain the tenuous thread of our theme we must turn again to a poet, Maximianus, who lived in the middle of the sixth century A.D., and who is known only from six elegies on old age (11). Coffman describes them as "lamentations on the ills of old age, inspired in the mind of the hero by memories of his youth and early manhood and by the realization of his failing powers in general and of his physical (sexual) impotence in particular. The first voices a prayer for death. The second is the pleading of an old man to his mistress to whom he no longer appeals, not to leave him, and a lament over his present impotency. The third and fourth are memories of the amorous thwarted experiences of his youth. The fifth is a sensual account of the highly erotic experiences of the old man with a young mistress and the lament of both over its ineffectual issue because of his old age. The last—only 12 lines in length, gives the final conclusion of the old man: Be reconciled to old age; be content that you are coming to the inevitable—death and the grave! In essence these elegies are a blending of lascivious eroticism, in degenerate Ovidian or Ausonian vein, and of universal cynicism and pessimism with a final touch of stoicism." The effect of old age upon the senses through loss of hearing, taste, sight, touch and smell, along with the colorless face, the dried-up skin and the rheumatic tears, is vividly described in Elegy I, pp. 119-150.

Coffman believes that this poem may have had a part in initiating certain clichés as a literary fashion, which were later improved upon by Pope Innocent III, in his *De contemptu mundi*, and afterwards popularized as a part of the stock in trade of Middle English descriptions of old age.

In retrospect we see clearly that to the problem of old age Rome contributed the medical influence of Galen, that in this field lasted far beyond Vesalius, and the contrasting views of Cicero the optimist, and Horace, who with Juvenal, spared no detail of the unpleasant side of the senium. The continuance of this narrative will reveal just how much farther we have advanced in our present thinking.

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- (7) See W. A. Falconer's preface to his translation of *De Senectute* in the Loeb Classical Library describing how he first rendered the essay into English for the pleasure of his 81 year old uncle.
- (8) HORACE: *Ars Poetica*, Conington's translation, London, G. Bell & Sons, 1905. For the benefit of the minority who still enjoy the classics in the original, we append the much quoted Latin verses:

"Multa senem circumveniunt incommoda, vel quod
 Quaerit et inventis miser abstinet ac timet uti,
 Vel quod res omnis timide gelideque ministrat
 Dilator spe longus, iners avidusque futuri
 Difficilis, querulus, laudator temporis acti
 Se puero, castigator censorque minorum."

- (9) COFFMAN, G. R.: *Old Age from Horace to Chaucer: Some Literary Affinities and Adventures of an Idea: Speculum*, 9: 249, 1934.
- (10) GARRISON, F. H.: op. cit. pp. 176-177.
- (11) The elegies were wrongly attributed to one Ca. Cornelius Gallus, as appears in the English translation by Sir Hovenden Walker, London, 1688, entitled "Elegies of Old Age made English from the Latin of Ca. Cornelius Gallus. (Coffman.)"

Carl Koller

December 3, 1857-March 21, 1944

As long as men study the past in order to understand the present and foretell the future, as long as medical history is written, Carl Koller's contribution to the conquest of pain will be remembered. Because of his many years of active work at The Mount Sinai Hospital, his passing gives us all a sense of personal loss, for here was an immortal that we knew as a colleague, here was a familiar figure, already become a legend, about whom future visitors will surely be told: "In this very spot, now used for the lockers of the visiting staff, was located the operating room of Carl Koller, the first to use cocaine in surgery."

Although he lived in New York City for fifty-six years, Koller's roots were in Austria and his training Viennese in the great tradition. He was born in Schuettenhofen, Bohemia in 1857, son of Leopold Koller and Wilhelmine Rosenbaum. Of his schooling we know only that he attended the *gymnasium* in Vienna, served his required term in the Austrian Army, and in 1882 received his medical degree from the University of Vienna. He did graduate work with Snellen and with Donders in Utrecht. Leaving Vienna to seek his fortune in the great world, he tarried briefly in London, where he met Dr. Ewing of St. Louis who encouraged him to go to New York City. There he arrived in 1888, already a famous figure, since his original paper on the use of cocaine in surgery published in 1884 when he was only twenty-six years old, had stimulated investigators all over the world.

In 1892 Koller married Miss Laura Blum of New York City whose companionship for over 52 years brought much happiness into his life crowded with achievement. He is survived by her and two children.

By 1901 he had become Adjunct Attending Ophthalmic and Aural Surgeon at The Mount Sinai Hospital under Dr. Emil Gruening, later heading the service as Attending Ophthalmic Surgeon. In this position he held sway from 1909 to 1920, when, having attained the stipulated age of retirement of 62 years, he became Consulting Ophthalmic Surgeon, which position he held until death. He was also Consulting Ophthalmologist to the Montefiore Hospital and to the Hebrew Orphan Asylum. Among the men who served under Koller at The Mount Sinai Hospital was Julius Wolff who followed him as the head of the service.

Great events and great discoveries seem often to stimulate the growth of legends which may even supplant the truth in the minds of later generations. There is already one rather fanciful account of Koller's contribution to be found in a work on the great pharmaceutical discoveries written for the general public. For this reason it is appropriate to retell the story in full.

When Albert Niemann discovered the alkaloid cocaine in 1860, his teacher, the great chemist Woehler, published in the *Annalen der Chemie in Pharmacie* (114: 216, 1860), his observation that the drug had a numbing effect on the tongue, but failed to realize the practical value of the observation. Moreno y

Mays was the first who proved the anesthetic action of cocaine in 1868. Later in 1879, the Russian investigator, V. K. Anrep (*Pflüger's Arch.*, 21: 38, 1880) injected the drug subcutaneously and observed that the skin over the area was insensitive to a pin prick. He definitely suggested that cocaine might be useful in surgery as a local anesthetic, but as far as is known, no one followed his advice. The summer of 1884 Sigmund Freud of Vienna, then not even on the threshold of fame, asked Dr. Koller to collaborate with him on a study of the physiological



Carl Koller
1857-1944

systemic effects of the drug. In the course of preparing for this physiological experiment, Koller realized that he had in his possession a local anesthetic. He at once went to Stricker's laboratory and instilled a drop of cocaine solution into the eye of a frog and afterwards into that of a guinea pig and found that the cornea and conjunctiva became insensitive to mechanical, chemical and other stimulation. He then repeated this experiment on himself, some colleagues and patients. He wrote a preliminary report of this work which was read at the Congress of German Ophthalmologists at Heidelberg in September 1884, by his

friend Dr. Brettauer, an Ophthalmologist of Trieste. (First publication, *Wien. med. Wehnschr.*, 34: 1276, 1884.) The effect of this paper on the audience is said to have been electrifying, since Brettauer readily demonstrated Koller's procedure to all interested.

In his original paper, Koller credits both Von Anrep and Freud, saying about the latter: "To us Viennese physicians cocaine has been prominently brought to our notice by the thorough compilation and interesting paper of my colleague at the General Hospital, Dr. Sigmund Freud." In his autobiography, Freud states clearly: "Koller is therefore rightly regarded as the discoverer of local anesthesia by cocaine. . . ."

Koller was the recipient of many honors for his great contribution. In 1922 the American Ophthalmological Society, of which he had been a member since 1889, bestowed upon him the first award of the Howe Medal. In 1929 the Heidelberg Medical Faculty honored him with Kussmaul Medal. In 1930 the New York Academy of Medicine made him the recipient of its Medal of Honor. The Medal of Honor of the American Academy of Ophthalmology and Otolaryngology was given to him in 1934. He was at one time an honorary member of the Ophthalmological Society of Heidelberg, the Royal Society of Medicine of Budapest and the Royal Academy of Medicine of Italy.

His bibliography includes contributions to the Transactions of the American Ophthalmological Society and to the Archives of Ophthalmology on such topics as blepharitis ciliaris and recurrent tuberculous choroiditis. He has also contributed articles on the genesis of his discovery to the International Anesthetic Research Society and to the Journal of The Mount Sinai Hospital.

It is abundantly clear from the foregoing that the fame of Carl Koller rests on the securest of historical foundations, although his early observations have been, in a measure, overshadowed and his pioneering work somewhat obscured by later developments in technique of local anesthesia and the use of cocaine substitutes.

The importance of this local anesthetic in eye operations can never be overestimated. It removed the hazards of sudden involuntary eye movement under the influence of pain or even the fear of it. It thus gave the surgeon a freedom of action he had never exercised before and this led to improved technique and boldness in developing new procedures.

The deep gratitude of thousands of patients and surgeons, especially those concerned with the care of the human eye, is a moving tribute and a lasting monument, a true memorial to Carl Koller.

PERCY FRIDENBERG, M.D.

Leo Arnstein

January 25, 1877–August 14, 1944

We meet today to pay our tribute to the memory of Leo Arnstein, who for forty-two years gave devoted service to this institution. Those of us who were privileged to be associated with him during a portion of this period and who learned to respect and admire him, have gathered informally to express our appreciation of his contribution to the growth and usefulness of this institution.

I believe that Leo Arnstein would have liked the simplicity of our gathering. He abhorred ceremony and ritual. He had no patience with elaborate eulogies. While he gave of himself to a great variety of philanthropic work, it was without fanfare and without self-sought publicity. And as he lived, so did he die. His expressed wish was that when the time came for him to leave this earth, there should be no public funeral and there should be no public announcements. His passing away should be in keeping with the manner in which he had lived.

It is only natural that those of us who knew him best admired him most. He was a man of great integrity. His honesty of purpose never could be questioned. He never would compromise a principle on which he had a profound conviction.

The tribute we pay his memory, by its very sincerity, is the finest proof of our appreciation of all the sterling qualities which he possessed. While this gathering today takes cognizance of the termination of his valiant service, the work he did will continue to be reflected in the policies and usefulness of the Hospital for years to come.

A resumé of his deeds and accomplishments will be made part of the minutes of this special meeting, so that those who follow will find inspiration and strength in learning of a man who had a keen appreciation of his responsibilities to the less fortunate in the land.

WALDEMAR KOPS.*

* * * * *

It is altogether fitting that we meet here for a few moments to adopt a resolution recording the work, services and death of Leo Arnstein. It is also fitting that some few words be said about him in the privacy of our meeting, although I am quite sure that by reason of his innate modesty and retiring attitude he himself would not want even this. We who knew him, however, feel that we have a claim upon him which entitles us to do this for ourselves and to contemplate briefly the life of a man who gave so much of himself to our Hospital.

There are many here who knew him well for many years. There are some who knew him only as they saw him as the President of our Hospital and as a Trustee, presiding at our meetings. It would be easy to put before you biographical material of a factual nature, but this is known to many of you and is

* Eulogy delivered at the Memorial Meeting at The Mount Sinai Hospital, September 19, 1944.

readily available to the others. Rather is it more fitting to inquire for a moment as to what kind of a man he was and what force motivated him to lead the fine life which he has just completed.

To those of us who only knew him briefly he was an austere man, at least at



Leo Arnstein
1877-1944

first meeting, with a rather cold exterior. Nothing could have belied his real personality more than this. In 1896 he was graduated from Yale University at the age of 19, having completed his course in three years, and was possessed of a burning desire to plunge into the career of medicine. Unfortunately, by

reason of circumstances beyond his control, this was not possible and he embarked upon a business career which throughout his life was not his vocation but his avocation.

What influences were at work which made him dedicate so much of his life to work for the community?

What incident furnished the turning point in his career and led him along this path?

These are the interesting things which make a man the kind of a man he is. Perhaps two people most influenced Leo Arnstein's life: his father and Lillian Vald, with whom he labored for many years in making the Henry Street Settlement the great institution it became. His father, a strict but kindly disciplinarian, imbued with his love for the Montefiore Hospital, guided Leo Arnstein in his early days to like interests in those who needed the help of their fellowmen.

Serious as he seemed to be, there was a side to him that only a few of his intimate friends learned anything about. He had the capacity to loaf, to enjoy leisure, to relish an anecdote, to enjoy a drink. He had a spirit of gaiety, could dance and make merry, "rib" his friends and mislead the gullible who at first acquaintance were themselves misled by his austere and dignified appearance. Unfortunately he did not indulge a great deal in enjoying life, as the term is popularly understood. He dedicated so much of himself and so much of his time to his efforts on behalf of this Hospital and the Henry Street Settlement, and to the many other activities in which he played a vital part, that there was little room in his life either for making money or for enjoying himself.

The Mayor of the City referred to him as "one of our city's finest sons." The Commissioner of Welfare told me that it was Leo Arnstein alone who kept his head on the Emergency Relief Board when there was a frantic struggle to handle the 350,000 families who were in desperate need. His calm and judicial temperament always provided a steadying effect and that is perhaps the reason why he was so often called to assist those who needed help in arriving at a decision. The poet says:

*"The world is too much with us; late and soon
Getting and spending we lay waste our powers."*

but not Leo Arnstein—getting and spending was not part of his life nor had he any taste for it. He might well have said with the same poet:

*"Great God! I'd rather be
A pagan suckled in a creed outworn,
So might I, standing on this pleasant lea,
Have sight of Proteus rising from the sea,
Or hear old Triton blow his wreathed horn."*

CARL AUSTRIAN.*

* Eulogy delivered at the Memorial Meeting at The Mount Sinai Hospital, September 19, 1944.

ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Management of Male Pubescence. W. A. SHONFELD. J. A. M. A., 121:177, January, 1943.

In this presentation the developmental aspects of pubescence presented in the first papers were used as a guide in the proper management of male pubescence from the developmental, endocrinological, and psychological viewpoints. Attention was drawn to the prolonged phase of genital latency during prepubescence and the great variations as to age of onset of pubescence. These often create a problem of differentiating the normal prepubescent from the eunuchoid. A test to prognosticate in prepubescence whether a boy will have spontaneous pubescence is based on the ability of the testes to respond to stimulation by chorionic gonadotropins of human pregnancy urine.

Induction of pubescence is the basis of nearly all endocrine therapy in this age group. The treatment varies only as to whether such endocrine products are used which stimulate the interstitial tissue of the testes to function (gonadotropins) or those which substitute for the hormones ordinarily secreted by the mature testes (androgens). The stage of pubescence to be induced also varies. Obesity and growth should be considered in their correlation with genital development and pubescence. The criteria used differentiated in the first group the prepuberal boy with obesity from the boy with true Fröhlich syndrome and in the latter group the short normal from the hypophyseal dwarf.

Pathology and Therapy of Stuttering. E. FROESCHELS. The Nervous Child, 2:148, January, 1943.

There is only one kind of sign present at the onset, this sign consisting of repetitions of syllables or of short words. It must be emphasized that initial iterations are characterized by a normal speed as compared with that part of the patient's speech that progresses normally. In this period of stuttering, no disturbance of the normal breathing, no accompanying movements, no signs of phobia are present. The iterations represent, at least at the very start, a kind of "filler" for missing words. Difficulties in the finding of words or word forms seem to be most characteristic for the ages of about 3 to 5 years; therefore stuttering starts most frequently at this time. The other signs that appear in more advanced stages do not emerge at the same time. But when they do appear, the signs already present do not vanish.

Thus far the following stages of development are known. Sooner or later the iterations are complicated by a pressure in those muscles of the speech apparatus that are engaged in the formation of the first of the sounds subject to repetition; e.g., ba-ba-ba is no longer spoken in a normal tempo, but the lips are closed firmly when the b's are pronounced. This produces a delay. If we term the iterations "clonus" and the pressure "tonus," then the combination of the two may be called "clonotonus" and "tonoclonus." It seems evident that the tonic component is due to an attempt on the part of the child to overcome the iterations, an attempt that obviously misses its aim. If clonotonus or tonoclonus arises, then breathing must begin to show abnormalities, since air cannot escape easily during the blockage. Clonotoni and tonocloni naturally delay the flow of the speech and therefore we call them slow tonocloni and slow clonotoni. With the tonic component accompanying movements (grimaces, stamping, etc.) appear. The tonic component comes more and more to the foreground, until the pure tonus results in a blockage, without repetitions, in the muscles of the larynx, the pharynx, or mouth.

The voices of stutterers in advanced stages are frequently soft and monotonous. Speaking during inhalation is a frequent occurrence in advanced stuttering. Sooner or later the picture of stuttering changes from more obvious signs to less dramatic ones (phase of "concealed" stuttering). Advanced cases frequently avoid difficult words by substituting other words. It seems that the progress from one sign to the next is due to an inner logic. At its beginning, the tonic component represents an attempt at overcoming the iterations. The accompanying movements, distracting the attention from the blocking speech muscles, are regarded as aids by the patients, and are later used as such. When older signs lose their effectiveness to overcome imaginary difficulties, they are partly replaced by new intentions. Rapid tonic cloni, rapid toni, rapid cloni, and slow cloni, are the remaining possibilities that the patient will exploit as new aids. The concealing stage finally is another invention, for "beautifying" purposes.

One kind of stuttering, namely, the traumatic type, shows a striking difference in development as compared with the development of the stuttering that we have discussed before. In the first world war, many hundreds of shell-shocked soldiers suffered from stuttering following their injury. All of them showed very early—as a rule they were admitted to the hospital a few weeks after the trauma—the triad of cloni (with or without tonic component), toni, and accompanying symptoms. In such cases, the stage of concealing appeared very soon.

Simplified treatment of acute tonsillitis. J. BERBERICH. M. Rec., 156: 35, January, 1943.

It has been again confirmed that an acute tonsillitis can be cured more rapidly by bismuth than by the other known remedies. Instead of intramuscular bismuth administration, sobisminol mass in capsules, administered by mouth or rectally, is for the first time introduced into the therapy of acute tonsillitis, pharyngitis granulosa and fusospirochetosis of the upper respiratory tract, such as Plaut-Vincent's angina and a specific tracheo-bronchitis. In adults 4-6 capsules of sobisminol are given on the first day of the disease and 3-4 on the second day. In children 3-4 capsules are given on the first day and 2-3 capsules on the second day. In the treatment of acute tonsillitis sobisminol shows no side-effects.

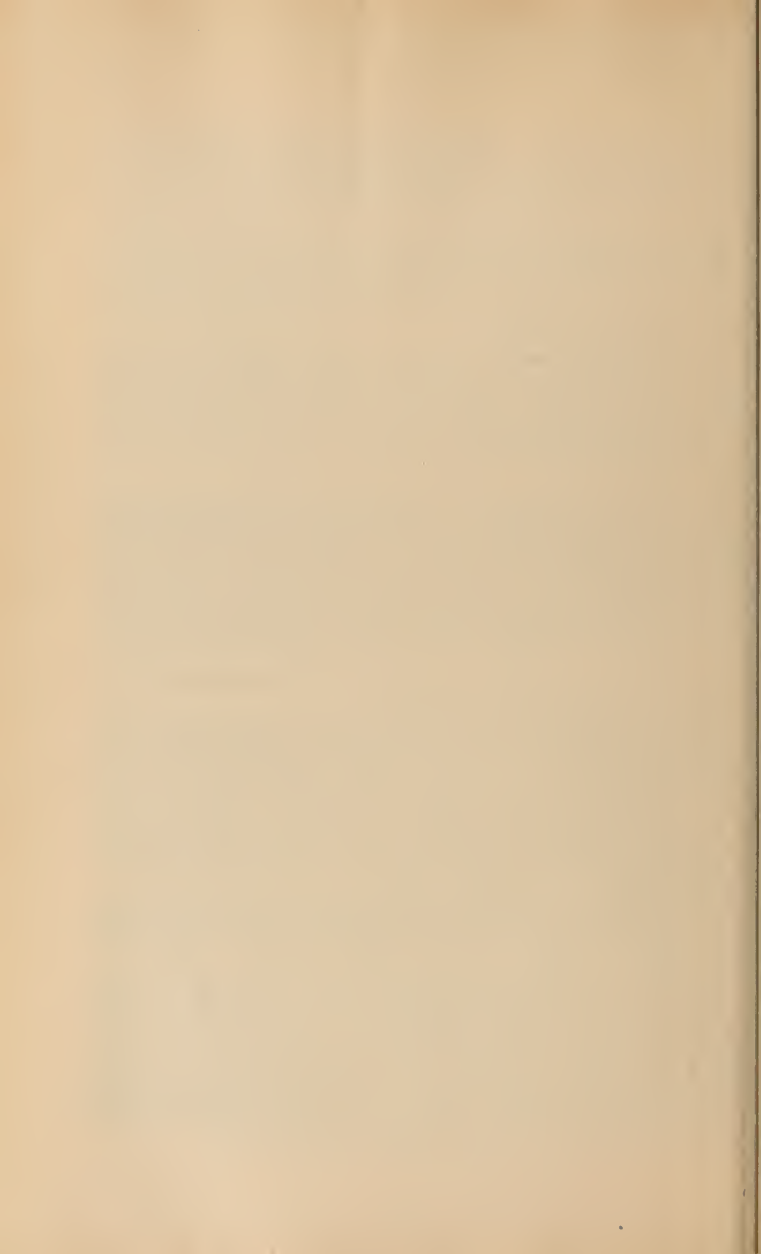
The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents.

R. OTTENBERG. Medicine, 22: 1, February, 1943.

Simple jaundice and acute atrophy of infectious origin are not unitary diseases, but may both be due to various viruses. The occurrence of a latent period before the appearance of jaundice is common to many infections, i.e., epidemic acute yellow atrophy, yellow fever and leptospirosis and poisons, i.e., chloroform, inorganic arsenicals, acriflavine, arsphenamines, cinchophens, sulfonamides, acetylene tetrachloride, dinitrophenol and trinitrotoluene. There is some evidence that functional and anatomic liver damage is already going on during the clinically latent period. A specific immunity follows several types of infectious jaundice: simple jaundice, yellow fever, spirochetel jaundice. In contrast is the greater susceptibility to many hepatotoxic agents after apparent recovery from jaundice due to a chemical.

Damage of the renal tubules is frequently associated with hepatic degeneration in: leptospirosis, yellow fever, transfusion of incompatible blood and other forms of acute hemolysis and poisoning with acriflavine, carbon tetrachloride, phosphorus, mushrooms and arsphenamines.

Critical analysis of the claims for allergy as the mechanism for liver damage from certain chemicals (cinchophens, arsphenamines, sulfonamides) shows that most cases fail to fulfill the criteria for allergy. Without present knowledge it is wiser to consider these as non-specific hypersensitivity, possibly on the basis of an abnormal metabolism or of a nutritional defect. Jaundice as a complication of burns has appeared only in the era of tannic acid therapy and may be related to it. Attention is called to a possible latent jaundice-producing virus in human beings as indicated by the occurrence of jaundice some months after the injection of attenuated yellow fever virus mixed with pooled human serum and likewise after the injection of measles prophylactic pooled human serum.



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RECENT ADVANCES IN HISTOCHEMISTRY¹

GEORGE GOMORI

[From the Department of Medicine, The University of Chicago, Chicago, Illinois]

Histochemistry, in a general sense of the word, means chemistry of the tissues. In this review, however, it will be used in a restricted sense, only those aspects of it being included which involve the use of the microscope in an attempt to localize morphologically certain chemical constituents of the tissues. Purely chemical studies of tissues or tissue components will not be mentioned. Histological staining techniques, the underlying chemical or physicochemical principles of which are not understood, will also be omitted.

Two years ago Gersh (1) in the *Physiological Reviews* gave a very extensive account of the progress of histochemistry during the past decade. To avoid unnecessary repetition I shall try to show the variety of chemical and physical principles employed in histochemical technique together with some of their results and practical uses rather than to give an all-comprising review of everything new that has happened in this field in recent years. For instance, the results of the application of long known methods to new problems will not be discussed.

The referral of chemical substances to morphological elements may be done in two ways. The first one is the direct visualization of the substance by some suitable chemical or physical means. The second one is the statistical comparison of results of chemical analysis and of quantitative microscopic examination of tissue samples.

I shall mention the methods of visualization first.

For a successful morphologic localization of chemical substances two conditions have to be fulfilled: first, the chemical substances to be demonstrated have to be confined to the sites they had originally occupied in the living tissue, and all displacement by diffusion or osmosis during the manipulation of the tissue has to be prevented; second, the physical or chemical means by which the chemical substance in question is detected must be applicable to tissue sections, and the picture obtained must be reasonably sharp and stable. In respect to the first point, there is no difficulty if insoluble or poorly diffusible substances such as fats or high-molecular protein-like substances have to be demonstrated. However, if easily soluble and diffusible substances have to be shown, the first and main problem is the prevention of displacement. This problem can be solved very well by the freezing-drying method, invented by Altmann (2) and perfected and reintroduced into microtechnique by Gersh (3). The principle of this method is the following: pieces of living tissue are dropped into liquid air or isopentane. At the temperature of these fluids—which is below $-100^{\circ}\text{C}.$ —

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the tissue will freeze immediately, and all liquid phases will become solid. The pieces now are dehydrated in high vacuum and at a temperature around -40°C . until they have completely lost their water. As there is no liquid phase present during the entire procedure, displacement of solutes by diffusion is impossible. The completely dehydrated pieces are embedded in paraffin without the use of any intermediate solvent that might permit diffusion. The paraffin blocks are cut into sections and floated on the reagent solution immediately. For chlorides, phosphates and carbonates a silver solution may be used, for potassium a solution of sodium cobalt nitrite. The precipitates that form at the sites where the respective ions were present can be further differentiated. For instance, silver carbonate and phosphate can be distinguished from chloride by the fact that they are soluble in dilute acetic acid. Potassium cobalt nitrite is recognizable both by its color and by the shape of its crystals.

Among the results obtained by this method the most important are:

1. Chlorine is present in the intercellular spaces of muscle cells only, whereas PO_4 and CO_3 are present both in the cells and in the intercellular fluid.
2. Potassium is present chiefly within the cells themselves.
3. The parietal cells of the gastric mucosa, which according to old theories were supposed to secrete HCl , could be shown to contain no chlorine ion.

If the substance to be demonstrated is not too mobile the only problem is the right chemical or physical means of demonstration. Many new chemical reagents have been described in the last 10 or 15 years which suit themselves admirably well for histochemical purposes. Most of them are organic. The other great advance made in this field is the utilization of fluorescence and of spectrophotometry in the microscopic examination of the tissues.

The substances that are demonstrable histochemically can be divided in four groups:

1. Elements.
 2. Organic compounds or groups of related compounds.
 3. Substances of which only the prosthetic groups can be identified.
 4. Enzymes.
- 1) *Elements*. All those to be mentioned here are metallic, with the exception of arsenic.

For the demonstration of calcium the good old method of Kóssa (4) still deserves preference. The more recently introduced lake-dyes such as alizarin red S, purpurin and kindred substances give similar but less brilliant pictures. However, alizarin red S has this great advantage: if injected *in vivo* it will selectively stain calcium salts which are deposited within one or two days after the injection. In this way it permits the study of bone apposition. Madder, used previously for the same purpose, gives far inferior results.

Among the heavier metals, the microtechnical demonstration of iron by the Prussian blue method is such an old and universally known procedure that it needs no comment. For copper the technique of Okamoto and Utamura (5), utilizing dithio-oxamide, gives excellent results. Copper compounds show up in the form of green-black granules. For lead, the technique of Sieber, (6) based on the formation of brown-black, acid resistant lead sulfide on treatment of the tissue with an acidulated H_2S solution, is satisfactory if the presence of

other heavy metals can be ruled out. For bismuth the reaction of Castel, (7) producing a bright red precipitate of brucine-BiJ₃ is highly specific. So is the reaction of Brandino (8) for mercury. It precipitates mercury in the form of a purplish blue Hg-diphenylcarbazide. Gold salts can be demonstrated by reducing them to metallic gold with SnCl₂ according to Christeller (9). There is an old method by Mendel and Bradley (10) for zinc, which, unfortunately, is not sensitive enough for use on vertebrate tissues. Arsenic can be detected by the method of Castel (11) which visualizes this element in the form of orange-yellow As₂S₃.

2) *Organic compounds.* Those for which a histochemical test is known form such a motley group that it is hard to deal with them systematically. The only system I shall adopt here will be their grouping under two headings: first, those demonstrated chemically; second, those demonstrated by physical means.

Urea can be detected by the very sensitive xanthidrol test, introduced into microtechnique by Oestreicher (12). As urea is extremely diffusible this test should be applied to frozen-dried material only if one wishes to avoid very considerable displacement. This, to my knowledge, has never been done. If the method is used in the customary way, on fresh tissues, it can merely indicate the presence of urea, without permitting any exact localization.

Ascorbic acid has the property of reducing silver nitrate even in an acid medium. This property is utilized by Giroud (13) who perfuses the organ with an acidified AgNO₃ solution and gets a black precipitate at the sites where ascorbic acid is present.

For glutathione, Joyet-Lavergne (14) treats fresh tissue sections with nitroprusside in an alkaline medium and gets the typical reddish sulfhydryl reaction. The color is very unstable and fades rapidly.

For bilirubin and bile pigments, Stein (15) oxidizes the section with iodine and gets a deep emerald green coloration due to biliverdin.

Cholesterol and some other steroids can be demonstrated with the digitonin reaction of Windaus (16). This reaction is given almost exclusively by steroids having a free OH group in position 3- α . Therefore, cholesterol, the vitamin D compounds, isoandrosterone, and others will yield a positive reaction, while progesterone and testosterone a negative one.

Riboflavin can be demonstrated by the technique of Chèvremont and Comhaire (17). The vitamin is reduced in an acid medium to leucoflavin and this leucoflavin is carefully reoxidized to rhodoflavin. Too energetic oxidation will destroy the colored compound. Riboflavin is demonstrated in the form of bright red granules.

About 15 years ago there was considerable interest in the distribution of arsphenamines in the tissues. Jancsó (18) devised a silver reaction for their demonstration. The specificity of this reaction is questionable, and it seems that it may demonstrate other reducing compounds alongside with arsphenamine.

The typical purplish metachromatic shade imparted to certain tissues, cells and granulations by a group of blue stains, such as thionin and toluidine blue and cresyl violet has been known for at least 30 years but there was no satisfac-

tory explanation for it until Lison (19) proved conclusively that it is due to sulfuric esters of high molecular weight. Typical representatives of this group of esters are heparin, chondroitinsulfuric and mucitinsulfuric acids. Lison was able to show that the metachromatic shade becomes increasingly reddish with increasing complexity of the organic group.

The methods so far mentioned were chemical. There are a few examples of physical methods playing an important rôle in histochemistry.

For instance, the fleeting green fluorescence of vitamin A in ultraviolet light, first observed by Querner (20), has proved to be specific enough for the study of this vitamin in the tissues. Jancsó (21) studied the distribution of anti-*protozoal* dyestuffs in trypanosomes. He found that acridine dyes attack selectively the blepharoplast. The other important but rather complicated and expensive method of histochemical analysis is microspectrophotography, developed especially by Caspersson (22). He could localize by this method the microscopic distribution of nucleic acid; and Gersh and Caspersson (23), with the same method, were able to study the distribution of thyroxine in the thyroid.

3) *Substances of which only prosthetic groups could be demonstrated.* Although the methods employed here lack the strict specificity of those in the previous group, their importance is still considerable and their results very encouraging.

The chromaffin reaction, known for over 50 years as specific for the cells of the adrenal medulla, for paraganglia and certain granulated cells of the gastrointestinal tract has been shown by Lison (24) and Clara (25) to be due either to two OH groups or to one OH and one NH_2 group in either ortho or para position on an aromatic nucleus. The substance giving this reaction and several others is probably not a single one but rather a group of closely similar ones.

In 1924 Feulgen and Rossenbeck (26) found that hydrolyzed thymonucleic acid gives an intense purplish coloration with Caro's reagent, fuchsine sulfuric acid. Subsequent studies on the mechanism of this reaction lead to the conclusion that a pentose, ribodeseose, is responsible for it. The reaction is very specific and can be performed on tissue sections. The nuclei will stain purple in a very selective manner.

Nine years later Bauer (27) discovered that many other carbohydrate-containing substances will give the same reaction if they are pretreated with chromic acid. To mention only a few of these substances: glycogen, cellulose, starch, mucin, tunicin. Without pretreatment with chromic acid these substances do not react with Caro's reagent. The exact mechanism of the reaction is still in the dark. For the time being it has to be assumed that chromic acid is able to set free aldehyde or keto groups which were hidden before oxidation. Bauer's stain is by far the best technique for the demonstration of glycogen and it deserves far more publicity than what it actually enjoys.

A group of German scientists of the Feulgen school (28) found that certain lipid substances, if exposed to air or treated with mild oxidants, will develop free aldehyde groups. They dubbed this hitherto unknown lipid aldehyde plasmal. Chemically it is a mixture of a number of long-chained aliphatic aldehydes, the bulk being stearic and palmitic aldehydes. Verne (29) described

a practical histochemical technique, based on Caro's reaction and gave excellent pictures of the results obtained. Plasmal is present in practically all tissues, especially in those which contain lipids other than neutral fats. The intensity and extent of the reaction depends on the amount of oxidative treatment the tissue is subjected to. Entirely fresh tissues, protected from air or fixed in formalin prepared with freshly boiled distilled water, are negative but on oxidation will show increasing amounts of plasmal, often in a most surprising pattern (figs. 1a and 1b).

Two or three years ago Bennett (30) reported that adrenals stained, after a mild oxidative treatment, with phenylhydrazine show a yellow layer in the outer layers of the cortex, due to hydrazone formation. This reaction can be prevented by extraction with ether or by pretreatment with semicarbazide. The author concluded from these results that he had demonstrated a lipid ketone,

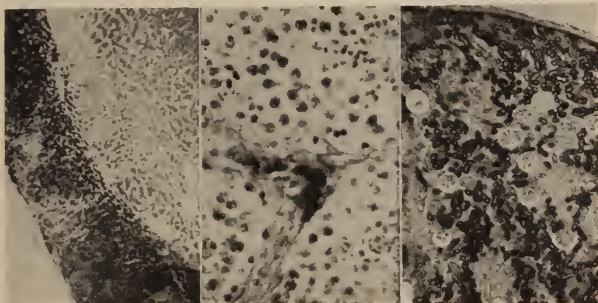


FIG. 1a. (Left) Non-endocrine adrenal cortical adenoma, compressing the adrenal cortex. Plasmal reaction positive (dark) only in the compressed cortex, negative in the tumor.

FIG. 1b. (Center) Plasmal reaction in the interstitial cells of the testicle.

FIG. 1c. (Right) Alkaline phosphatase picture of the normal guinea pig kidney.

probably a ketosteroid. The papers of the Feulgen group apparently escaped his attention since he made the statement that no lipid aldehydes are known to exist in the adrenal cortex. On studying the pictures he had published I became suspicious that the new reaction demonstrates plasmal rather than ketosteroids. To prove this contention I took a large number of adrenals and other tissues containing lipids, such as brain, necrosing tumors and the like. The pieces were fixed in formalin, halved, and one cut surface treated with phenylhydrazine, the other one with Caro's reagent. The pictures obtained were invariably mirror images, except for the shade. In addition, when the tissues were carefully protected from oxidation, both Caro's and the phenylhydrazine reaction were entirely negative. This is, as far as I can see, a conclusive proof that the phenylhydrazine test is by no means specific for ketosteroids (31) although the cause of the almost invariably positive plasmal reaction at sites where the presence of ketosteroids is a known fact, remains a puzzle.

4) *Enzymes*. Methods for the demonstration of some of the enzymes have been known for the last 40 years, but the group included only oxidative enzymes such as peroxidase, phenol-oxidase and dopa-oxidase. The methods for this group of enzymes are fairly good in their original forms and hardly need any improvement. I wish to mention only one new method because it is vastly superior to methods used previously for the same purpose. It is the peroxidase reaction of Lison (32) which should completely supersede the old and very unsatisfactory benzidine stain of Lepehne (33). It is based on the fact that the leuco-bases of certain sulfonated acid dyes such as acid fuchsin, acid violet or patent blue are rapidly reoxidized to their highly colored dye forms by the system peroxide-peroxidase. Lison's reactions are extremely sharp and specific.

The first method to be described for a hydrolytic enzyme is that of Sen (34) for urease (1930). The tissue is incubated with a solution of urea containing some soluble cobalt salt. At the sites of urease activity CoCO_3 will precipitate which can be shown by subsequent blackening by H_2S .

In 1935 Semenoff (35) published his method for succinic dehydrase. He stains a frozen section of fresh, unfixed tissue in a mixture of sodium succinate and methylene blue. The section is then placed on a slide, covered with a coverslip the edges of which are sealed airtight. Fading of the methylene blue stain indicates the presence of succinic dehydrase. Boiled tissue does not give this reaction. According to Semenoff, in the liver the highest concentration of the enzyme is around the central veins, whereas in the intestine it is in a layer just below the covering epithelium.

In 1939 Takamatsu (36) and I (37) simultaneously published practically identical methods for the demonstration of alkaline phosphatase in tissue sections. The method is based on the fact that phosphatase is an extremely hardy enzyme. It will resist alcohol and all other dehydrating agents as well as exposure to the temperature of the paraffin oven, provided it is completely dehydrated. Paraffin sections are incubated in a solution of calcium glycerophosphate, buffered at pH 9. At the sites of phosphatase activity a precipitate of calcium phosphate will form which can be demonstrated either by Kóssa's method or by transforming it first into cobalt phosphate and subsequently into black CoS .

The results of this stain are highly interesting. Many normal tissues show an extremely typical phosphatase picture the biological significance of which is not known. However, it seems that, among other tissues, those which are involved in the absorption or excretion of carbohydrate are phosphatase positive. The entire epithelium of the gastrointestinal tract from the duodenum downward, the epithelium of the convoluted renal tubules (fig. 1c), the secretory cells of the lactating mammary gland are intensely positive. On the other hand, the renal tubuli of aglomerular fishes which are unable either to excrete or to absorb glucose are negative (38). Kidneys with greatly reduced function also lose part or all of their phosphatase activity (fig. 2a). Although I do not have enough cases yet to draw a definite conclusion, my experience thus far shows that one can judge the function of a kidney with fair accuracy on the basis of its phosphatase picture. Sites where calcium salts are deposited, with certain excep-

tions, are also intensely positive, thus indicating a possible rôle of phosphatase in calcification. A very interesting observation is the extreme riches of true osteogenic sarcomas in phosphatase. I have studied about 15 cases of osteogenic sarcomas all of which were intensely positive, whereas a motley group of about 30 sarcomas of other kinds, including fibrosarcomas, chondrosarcomas without bone production, myelogenous tumors and the like were all negative, no matter whether they did or did not originate from bone. Round-cell bone sarcomas, usually diagnosed as Ewing's tumors or reticulum sarcomas, fall into two distinct groups, indistinguishable otherwise, the one being intensely phosphatase-positive, the other entirely negative. I do not know what significance should be attached to this finding.

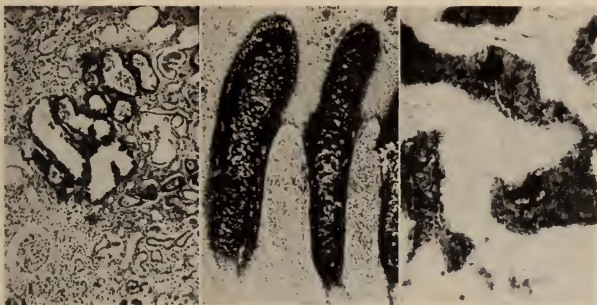


FIG. 2a. (Left) Alkaline phosphatase picture of a kidney from a case of chronic glomerulonephritis. Only a group of dilated tubules are positive; the remainder are negative.

FIG. 2b. (Center) Calcification of embryonic ribs. Calcified tissue black; zone of phosphatase reaction, dark gray.

FIG. 2c. (Right) Calcification of tubercles in the rabbit. Calcium salts are deposited in the centers of phosphatase-positive areas.

To study the relationships between calcification and the presence of phosphatase I had to modify my previous technique which stained preformed deposits of calcium salts and sites of phosphatase activity in the same shade. The modified technique (39) is the following: The sections are first treated with a solution of cobalt acetate which will transform calcium phosphate and carbonate into the corresponding cobalt salts. They are subsequently blackened by a solution of H_2S . The sections pretreated in this way are now incubated with calcium glycerophosphate. The new deposits of calcium phosphate that form at the sites of enzyme action are transformed into lead phosphate and stained red by acridine red. Counterstain is methyl green. Results: preformed calcifications, black; sites of phosphatase activity red; nuclei, blue-green.

Some of the results obtained by this method are as follows:

1. Calcification of bone, both embryonic and later, invariably starts in phosphatase-positive areas (fig. 2b). The same applies to bone produced by osteogenic sarcomas.

2. Calcification of caseated tubercles in the experimental tuberculosis of the rabbit also starts in the centers of phosphatase-positive areas (fig. 2c). Non-necrotic tuberculous granulation tissue itself is negative for phosphatase.

3. Certain types of calcification, such as calcification occurring in hyaline connective tissue, take place without phosphatase activity.

For acid phosphatase the above method is unsuitable for several reasons. First of all, alcohol, the fixative used for alkaline phosphatase, destroys the acid variety. Second, at pH 5, the optimum pH for acid phosphatase, calcium phosphate is easily soluble and will not precipitate. Therefore, for the demonstration of this enzyme a suitable fixative and a metal, nonpoisonous for the enzyme and having a phosphate insoluble at pH 5, had to be found. After a series of trials and errors it was found that ice cold absolute acetone preserves acid phosphatase

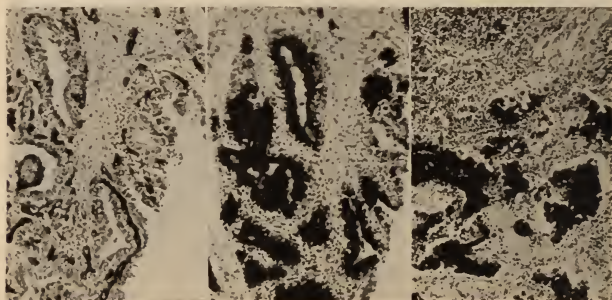


FIG. 3a. (Left) Alkaline phosphatase picture of the adult human prostate. Capillaries are positive; glandular epithelium is negative.

FIG. 3b. (Center) Acid phosphatase picture in next serial section of the same prostate. Capillaries are negative; glandular epithelium is intensely positive.

FIG. 3c. (Right) Metastasis of a prostatic carcinoma in an inguinal lymph node. Nests of tumor cells are positive for acid phosphatase.

very well, in fact, makes it resistant to alcohol and other chemicals used in the embedding process. As to the right metal, there are two metals which have phosphates insoluble at pH 5, lead and uranium. Uranium was found to be rather toxic for the enzyme whereas lead had very little effect on it. Therefore the final solution of the problem (40) was fixation in chilled acetone and incubation in a solution of lead glycerophosphate buffered at pH 5. The resulting white precipitate of lead phosphate is transformed for better visibility into black PbS. The distribution of acid phosphatase is entirely different from that of alkaline phosphatase. It is present in some curious locations; the biologic significance of its distribution is another puzzle. Tremendous amounts are found in the epithelium of the adult prostate gland (figs. 3a and 3b) and in all tumors arising from adult prostatic epithelium. Metastases from a cancer of the prostate can be recognized by their high acid phosphatase activity (fig. 3c).

Acid phosphatase is not found around sites of calcification.

In conclusion of this review I should like to give a short account of an entirely different approach to the localization of chemical substances, especially enzymes, in the tissue— I am referring to the extremely ingenious methods of Linderstrøm-Lang (41). The fundamental principle of his method is the statistical comparison of data of chemical analysis with those of careful quantitative microscopic examination done on many comparable samples of tissue. Technically this is carried out in the following way: Tissues are frozen solid, and a plug of tissue, about 2 to 3 mm. in diameter, is removed with a cork borer. This plug of tissue is mounted on a freezing microtome of special construction, permitting serial cutting of sections of very uniform thickness. Now alternate sections are used for chemical determination and microscopic examination. Let us have an example. We want to localize the site of pepsin production in the gastric mucosa. A plug of the gastric mucosa, including all layers of it from the surface down to the muscle layer is removed and sliced in a continuous series of sections about 20 micra thick. Alternate sections are mounted on slides and stained with routine histologic methods. The number of cells of each cell type is carefully counted in every section, and the data obtained are plotted on a chart, the abscissa being the distance from the surface. A typical population curve is obtained for each cell type. Now on the sections in between a careful microdetermination of pepsin is done, and the results are plotted in a similar way. By comparing the curve of enzymatic activity with the curves of the various cell types it is found that enzymatic activity follows exactly the number of the so-called chief cells and of no other cell type. In this way the conclusion that the site of pepsin formation is the chief cells seem to be entirely valid. Some other enzymes were localized in a very similar way; among others, dipeptidase, urease and arginase. Of course, the microtechnical methods had to be adapted to minute quantities of enzymes. I cannot go into details but suggest to those interested in this really ingenious piece of work to read the original papers of Linderstrøm-Lang.

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WOUND INFECTIONS IN DIABETIC SURGICAL PATIENTS

ANALYSIS OF THIRTY-FOUR CASES

RALPH W. WATSON, M.D.¹

[From the Surgical Service of Dr. John H. Garlock]

In the series of cases herewith reported, it was found that the incidence of wound infection as a complication following surgery in the diabetic patient, was greater than has been reported by previous writers on the subject.

During the period from July 1, 1937 to July 1, 1939, inclusive, thirty-four patients, all presenting a history of preceding diabetes mellitus, were operated upon for some pathologic condition having no direct relation to their glycosuria, Johnson (1) in his discussion of diabetes in relation to abdominal surgery, states: "The normal surgical misadventures of life equally bestrew the path of the diabetic, as the non-diabetic, irrespective of his underlying malady."

With the exception of two thyroidectomies and one hernioplasty, every patient was subjected to laparotomy. The operations were done by six surgeons. Of the thirty-four operations, 15 or 44 per cent of the wounds healed by primary union; 19 or 56 per cent of the wounds became infected. In each of these cases, the diabetes was well controlled by dietary restrictions and the use of insulin, before any surgical procedure was attempted.

The resistance of the tissues to infection in diabetics, is much lower than in individuals without glycosuria. This fact is widely accepted. Trimble and Carey (2) found that the average true sugar content of skin and muscle in non-diabetic subjects, was 56 and 28 mg. per cent respectively; whereas for diabetics the corresponding average values were 144 and 51 mg. per cent respectively; but the average true sugar of the whole blood was 226 mg. per cent. Thus, the elevation of sugar concentration in the blood was accompanied by a marked absolute increase in the quantity of sugar in the skin, while the elevation in the muscle was much smaller. Poor blood supply, due to atherosclerosis or endarteritis of the smaller vessels, may cause local ischemia. It has also been stated that the tissue cells in these patients are flooded with an excessive amount of glucose. These factors produce an excellent medium for infection. Morris (3) reports: "Sugar in the blood is hygroscopic, removes water from the tissues, and obstructs repair; and also, the tissue fluids contain sugar, and are good culture media."

The resultant infection may spread rapidly and may be accompanied by local gangrene. Whereas this sequence of events occurs not infrequently in the lower extremities, and occasionally in the upper extremities, it may also take place on the abdominal wall. Although obvious infection may not exist, there may be delayed wound healing. It is a well known fact that wounds in the diabetic patient not infrequently take longer to heal than those in non-diabetic individuals.

¹ Captain, U.S.A., M.C.

In summarizing the various factors which may be the cause of the lowered resistance to infection in the diabetic, Marble (4) noted the following:

1. Increased sugar content of blood and tissues.
2. Decreased activity of the blood elements associated with resistance to infection: a) subnormal activity of complement: b) subnormal phagocytizing capacity of leucocytes; c) subnormal bacteriostatic and bactericidal action of the whole blood.
3. Inadequate functioning of fixed tissue cells.
4. Lowered capacity of tissues to react to antigenic stimuli.
5. Lowered state of general cellular nutrition.

Cohen (5) states: "No class of patients is more prone to surgical complications, has less tendency to recover, and is less resistant to toxic infection than the diabetic."

There are many factors which may predispose to wound infection in the normal or non-diabetic patient. Maingot (6) lists the following:

1. Inadequate pre-operative skin preparation.
2. Inadequate protection of the wound during the operation.
3. Excessive tissue trauma, a very common cause.
4. Imperfect hemostasis.
5. The nature of the operation: Infection is particularly prone to occur after operations on the stomach, duodenum, biliary tract or colon, and in all cases of peritonitis whether localized or generalized.
6. Unsuitable sutures and ligatures, mass ligation.
7. Laxity with regard to pre-operative preparation of the surgeon, assistants and nurses.
8. A crowded operating theatre, or the casual spectators who have not previously dressed themselves in the usual operating room outfit.
9. Streptococcus carriers. Both nose and mouth should be adequately covered (the entire operating room personnel) to prevent against this source of wound contamination.

When this impressive list of factors influencing the infection of operative wounds in normal individuals is added to the inherently low resistance of diabetic tissues, the greatly increased risk becomes apparent.

In the group of cases herewith reported, ten operations were on the biliary tract, and fourteen on the intestinal tract. The remaining ten cases consisted of the following:

- Thyroidectomy—2
- Hernioplasty—1
- Appendix abscess—1
- Abdominal wall lipectomy—1
- Splenectomy—1
- Excision of diverticulum of cervical esophagus—1
- Exploratory laparotomy for inoperable carcinoma of stomach—1
- Exploratory laparotomy for inoperable carcinoma of gall-bladder—1
- Exploratory laparotomy for generalized carcinomatosis—1

In the ten operations on the biliary tract, 3 or 30 per cent healed by first intention, and 7 or 70 per cent developed wound infections (Table 1). Of the fourteen operations on the intestinal tract, 7 or 50 per cent had clean wounds and 7 or 50 per cent had infected wounds. In the remaining ten cases, 5 healed by primary union, and 5 became infected.

As previously stated, the incidence of wound infection in this series of cases was 56 per cent. This is much higher than other authors report. Parsonnet (7) states: "With the exception of six cases, wounds healed by primary union within the same period as compared with non-diabetics" (series of 56 cases). Noble (8) reports "of the seven cases operated upon by myself, six made good

TABLE 1

Type of operation	Total number cases	DIABETICS				NON-DIABETICS			
		Clean wounds		Infected wounds		Clean wounds		Infected wounds	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
All operations.....	34	15	44	19	56	31	91	3	9
On biliary tract.....	10	3	30	7	70	9	90	1	10
On intestinal tract.....	14	7	50	7	50	12	86	2	14
Other operations.....	10	5	50	5	50	10	100	0	0

TABLE 2

Type of operation	Total number cases	DIABETICS				NON-DIABETICS			
		Clean wounds		Infected wounds		Clean wounds		Infected wounds	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
All operations.....	34	15	44	19	56	31	91	3	9
On biliary tract.....	10	3	30	7	70	9	90	1	10
On intestinal tract.....	14	7	50	7	50	12	86	2	14
Other operations.....	10	5	50	5	50	10	100	0	0

recoveries and one died in diabetic coma. In the six remaining cases, the healing of wounds and the general progress of the patients toward recovery were not any different from those patients not the subject of glycosuria." The experience on this service in this respect, is not quite so favorable.

The wounds in this series of cases were closed in one of five different ways. The thyroids and the hernia were closed in layers, with metal clips for the skin. These wounds healed by primary union. The remainder of the wounds were sutured as follows: 21 were closed in layers with interrupted silk sutures for the skin; 9 or 43 per cent healed by primary union (Table 2) and 12 or 57 per cent suppurated. Five cases were closed in layers, with silk-worm gut tension sutures down to, but not including peritoneum. Of these, 1 or 20 per cent healed by first intention, and 4 or 80 per cent became infected. Four cases were

closed with through and through sutures of silk-worm gut, down to and including peritoneum. No other sutures were used in these cases. One wound, or 25 per cent, healed by primary union, and 3 or 75 per cent became infected. The one case that was left wide open and packed, healed without evidence of infection.

A comparative study of operative wounds of non-diabetic surgical patients was made for control purposes. An equal number of cases, thirty-four, were studied. These cases were chosen with the following requirements in mind:

1. Operation must have been performed during the same period—July 1, 1937–July 1, 1939, inclusive.
2. Surgeons were the same six men who had operated on the thirty-four diabetic patients.
3. The cases must present as closely as possible, the pathological and surgical features presented by the diabetic patients.

It is felt that the selected cases represent a fair cross-section of the non-diabetic material on this surgical service.

Of the thirty-four cases selected, 31 or 91 per cent healed by primary union, and 3 or 9 per cent developed wound infections. There were ten operations on the biliary tract. Nine patients or 90 per cent had an uncomplicated postoperative course as far as the wound was concerned. In 1 or 10 per cent, an infected wound resulted. Some type of intestinal operation was performed on fourteen patients. Twelve or 86 per cent had clean wounds, and 2 or 14 per cent suppurated. The ten remaining cases healed by primary union.

Regarding the wound closure in the non-diabetic cases, the two thyroids and one hernia, closed in layers with metal clips for the skin, healed by primary union. Of the twenty-one cases closed in layers with interrupted silk sutures for the skin, 20 or 95 per cent were clean, and 1 became infected. In the five wounds closed in layers, with silk-worm gut tension sutures down to peritoneum, 4 or 80 per cent healed *per primum* and 1 or 20 per cent became infected. Of the four wounds closed with through and through silk-worm gut sutures, going through peritoneum, 3 wounds or 75 per cent healed by first intention. One wound became infected. The one wound left wide open and packed was clean.

It is important to stress that the majority of operations performed in both series, 25 or 71 per cent, were on the biliary and intestinal tracts, in which groups infection is particularly prone to occur, as emphasized by Maingot.(6). A comparison of these two groups with this in mind shows that, in the diabetic group of intestinal and biliary tract cases, 58 per cent became infected, while in the control series 13 per cent suppurated.

CONCLUSION

A comparison of these two groups of patients, one diabetic and the other non-diabetic, indicates that postoperative wound infection is six times more frequent in the diabetic group. All other factors being equal, we are forced to the conclusion that this susceptibility is in large part due to the greatly lowered tissue resistance inherent in the diabetic patient.

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GLIOMA OF THE OPTIC NERVE¹

HERBERT M. KATZIN, M.D.

[*New York City*]

Glioma of the optic nerve has been described but three hundred times in the literature. It offers problems of interest to the many branches of medical science that are concerned with the crossroads of the visual pathways, the chiasm.

The classical clinical picture occurs in young children; it consists of slowly progressing proptosis, deterioration of vision, impairment of mobility of the eyeball, and papilledema or atrophy of the nerve. The optic foramen is enlarged roentgenologically. Backward extension leads to involvement of the chiasm, with loss of vision in the other eye. Pressure on the diencephalic centers may lead to disturbance of the vegetative nervous system, or to obstruction of the third ventricle. The tumor grows by direct extension, remains within the confines of the dural sheath, never metastasizes.

Ophthalmologists have been prone to regard glioma of the optic nerve as a congenital, slowly growing benign tumor. Examination of the literature reveals that it probably is of congenital origin, that growth is usually slow, but may be rapid, and that its course is by no means benign in most instances. Many of the cases reported have been in conjunction with von Recklinghausen's disease.

Byers (1902) reviewed 102 cases and added two of his own. He considered the neoplasm to be of mesoblastic origin, best to be defined as "fibromatosis."

Hudson (1912) concluded that these tumors arise from neuroglia within the nerve stem, consist of a generalized overgrowth of neuroglial tissue of infiltrative character.

Verhoeff (1922) confirmed Hudson's view, and added that almost all of the primary intraneural tumors of the optic nerve are gliomas.

Von Hippel (1923) considered proliferation of the glia as the most important factor, but noted that in many cases there is also proliferation of connective tissue within the nerve sheath.

Goldstein and Wexler (1932) described a case associated with von Recklinghausen's disease, in which the tumor was described as a spongioneuroblastoma.

Lundberg (1935) described ten cases, nine of which were gliomas of the oligodendrocytoma type, and one was a meningiopsaminoma.

Davis (1940), in an excellent paper, reviewed the literature to date and added five cases of glioma associated with von Recklinghausen's disease. His study indicated that "glial tumors start with an abnormal proliferation of the normal adult types of neuroglia of the nerve stem. After varying periods of growth the abnormal neoplastic neuroglial cells penetrate the pia, with the formation of a gliomatous tumor in the sheath. Proliferation of the mesothelial cells of the arachnoid follows the glial penetration of the pia, with the formation of a tumor-

¹ From the Ophthalmological and Neurosurgical Service, The Mount Sinai Hospital, New York, New York.

like mass in this portion of the nerve sheath. Later, intermingling of the proliferated cells from these two areas produces a complex histologic structure. The following types of gliomas have been reported: spongioblastoma, spongioneuroblastoma, astrocytoma and oligodendrocytoma.

Dandy (1941) described four cases of this tumor, all in young children. All showed widespread involvement of chiasm, optic nerves, orbits and brain. In one instance the tumor extended through the third ventricle and the temporal, frontal, parietal and occipital lobes on one side. These cases were considered to be astrocytomata. All were inoperable.

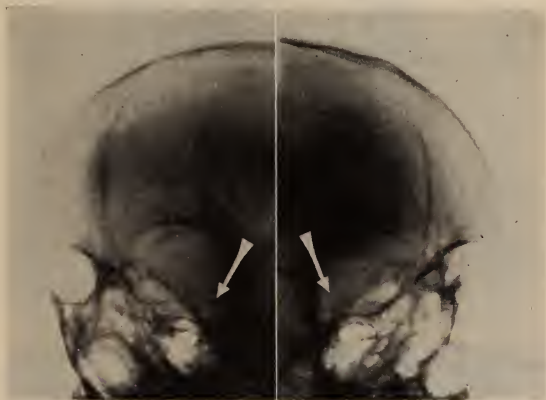


FIG. 1. X-ray visualization of the optic foramina, showing enlargement on the right side

CASE REPORT

History: R. B., (Adm. #509204) a girl, 7½ years, was admitted to The Mount Sinai Hospital on August 10, 1943. There was nothing pertinent in her past or family history. Three weeks prior to admission, swelling of the right upper eyelid was noted. This subsided within a week, but the child complained of loss of vision. In addition, there were anorexia, pallor, listlessness, low grade fever, and a five pound loss of weight.

Examination: On admission, both lids of the right eye were slightly edematous, there was proptosis on that side of 2½ mm., and the eye was totally blind. Consensual pupillary reflexes were present, but none on direct stimulation. Mobility of the eye was impaired, indicating paresis of the right external rectus, inferior oblique and superior rectus muscles. Examination of the fundus disclosed papilledema of about 5 diopters, with many small hemorrhages on the surface of the disc. There was peripapillary retinal edema, the veins were tortuous and engorged, the peripheral retina normal. The left eye was normal in every way, including visual field examination.

Laboratory Data: Laboratory findings of significance included a markedly positive tuberculin test. X-ray examination of the orbit, outlined with the aid of injected air, revealed no abnormality. X-rays of the optic foramina showed slight enlargement on the right side.

Operation: (Dr. Ira Cohen) Under novocaine infiltration anesthesia, a coronal incision was made in the scalp, and a low frontal flap turned outward. The right lateral ventricle

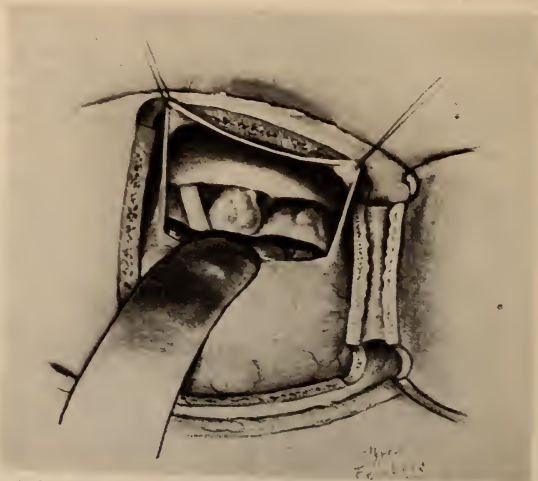


FIG. 2. Sketch of the operative field, showing tumor of the right optic nerve

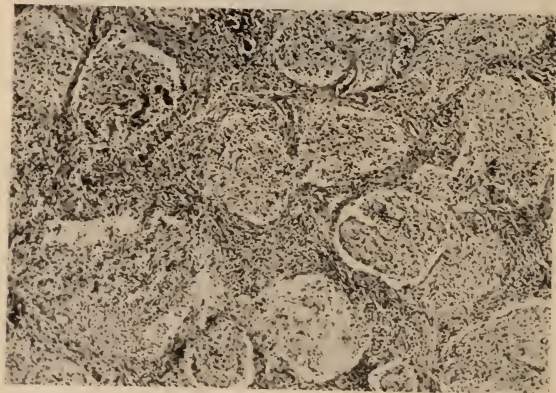


FIG. 3. Section of biopsy specimen

was aspirated, 40 cc. cerebrospinal fluid was removed, and the dura opened. The frontal lobe was then elevated, disclosing the optic nerves. The left nerve appeared to be normal, but the right optic nerve was thickened four to five times its normal size, from optic foramen

to chiasm. Since the chiasm was also involved, removal was not performed. A biopsy was taken, and the wound closed in layers. The operation was completed under local anesthesia.

Pathology: Biopsy material was reported as follows by Dr. J. H. Globus: "No gross material was seen by the examiner, who reports on the histologic findings. The latter disclose that the material is in all probability a cross section through a nerve. The microscopic field exhibits a large number of thickened and fairly dense trabeculae breaking up the microscopic field into numerous compartments. These compartments contain tissue in various phases of preservation or disorganization. The best preserved compartments seem to contain glial tissue, while those which have undergone, disorganization show remnants of badly preserved glial tissue. Within the trabeculae there are numerous blood vessels. The trabeculae are probably made up of collagenous material. Diagnosis: Gliogenous material duplicating the appearance of a nerve trunk. This is in conformity with the clinical diagnosis of glioma of the optic nerve."

Course: The patient remained in the hospital for nine weeks. During this period she received a course of radiotherapy directed to the right optic nerve.

Some degree of light perception returned to the involved eye several weeks after the inception of radiotherapy, and the papilledema receded, leaving an atrophic nerve head. Her general health improved somewhat, including a gain of ten pounds in weight.

SUMMARY

A case is reported of glioma of the optic nerve, with operative exploration, biopsy, and treatment. The progressive nature of this neoplasm is stressed, and its frequent association with von Recklinghausen's disease noted. The apparent benefit derived in this case from radiation may be temporary. If it proves to be lasting, the observation is a significant one. Most cases are found to be inoperable.

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ACUTE SUPPURATIVE LABYRINTHITIS AND BACTERIAL MENINGITIS, LABYRINTHECTOMY RECOVERY

REPORT OF A CASE

JOSEPH G. DRUSS, M.D.

[From the Otologic Service of Dr. J. L. Maybaum]

The management of patients with labyrinthitis secondary to middle ear supuration has always been a difficult problem for the otologist. This can be attributed to three chief causes, (1) the threatening danger of an intracranial complication is ever present (2) the exact nature of the inflammatory process within the labyrinth cannot always be ascertained by clinical tests and (3) a decision for or against operative interference is not infrequently made with great difficulty, since, on the one hand, meningitis may be provoked by too early operation, while on the other, it may be brought about by undue delay in operation. With the advent of chemotherapy, however, our fears of otitic meningitis have been somewhat allayed in the realization that this complication can be averted not infrequently by prophylactic measures or controlled satisfactorily when it does occur. Nevertheless, we are still of the opinion that the appearance of meningeal signs in the course of a labyrinthitis is of serious importance and is a definite indication for operation upon the labyrinth. Under certain circumstances, however, it is considered more expedient to treat the meningitis first, deferring operation until the meningitis is under control. This, as well as other points of interest, is illustrated by the following case report.

History (Adm. #514325): J. J., male, aged 57 years, was admitted to the Otologic Service of The Mount Sinai Hospital, on December 17, 1943. Two weeks earlier he had an infection of the upper respiratory tract, and in two days there developed pain behind the left ear which began to discharge spontaneously on the tenth day of the illness, and in another day there appeared weakness of the left side of his face. Significant in the past history was the occurrence 19 years ago of a facial paresis on the right (opposite) side associated with a right otitis media in the course of a bronchopneumonia. The facial paresis and the otitis media at that time resolved spontaneously in one week.

Examination. On admission otologic investigation disclosed a profuse purulent pulsating discharge from an anterior perforation of the left tympanic membrane. The remainder of the drum was full and there was a suggestion of sagging of the superoposterior bony canal wall. Slight tenderness over the mastoid was elicited and the hearing was impaired to whispered voice. The fistula test was negative. The right drum head was slightly thickened but otherwise negative and the hearing in the right ear was normal. Spontaneous nystagmoid jerks on looking to the right were noted.

The general physical examination was essentially negative except for a blood pressure of 190 systolic and 110 diastolic. The laboratory findings included: a blood count of 9,900 white blood cells of which 67 per cent were polymorphonuclear leukocytes; hemoglobin, 82 per cent. The blood Wassermann test was negative. Roentgen examination of the mastoids disclosed a diffuse clouding of the cells with intact trabeculi on the left side. There were no abnormalities on the right side.

Course. While the patient was under observation the postauricular pain and tenderness increased in severity, the temperature rose to 100.6°F. The facial paralysis showed no sign

of improvement. A simple mastoidectomy was performed and a suppurative mastoiditis was encountered. A large cell in the region of the fallopian canal between the posterior canal wall and jugular bulb when opened yielded pus under pressure; the fallopian canal itself was apparently intact.

The postoperative course was uneventful for the first 6 days when suddenly the patient began to experience headache and dizziness. Examination revealed an intermittent nystagmus in both horizontal planes and a bilateral equivocal Kernig sign. The temperature rose to 101.2°F. A lumbar puncture yielded clear cerebrospinal fluid under increased pressure. Within 8 hours after the onset of the acute symptoms frank signs of meningitis appeared including stupor, nuchal rigidity, bilateral Kernig, and a positive Brudzinski sign. The cerebrospinal fluid was cloudy containing 10,500 cells per cm., all polymorphonuclear leukocytes. The Pandy test was 4 plus. Pneumococcus type III was found on culture.

Large doses of sulfadiazine, supplemented by glucose in saline and sodium lactate were administered intravenously. The response to the drug was almost immediate and highly satisfactory, the meningeal signs completely subsiding and the patient fully regaining consciousness within a period of 24 to 36 hours.

Because of the presence of dizziness and nystagmus at the onset of the meningeal invasion a diffuse suppurative involvement of the labyrinth was strongly suspected and established with a reasonable degree of certainty when a total loss of function of the cochlear and vestibular branches of the 8th nerve was found on tuning fork and caloric tests. These tests also aided in establishing the labyrinth as the most likely route of extension of the infection from the tympanomastoid to the meninges. Neurological examinations failed to show any signs pointing to a focal expanding lesion in the brain.

A radical mastoidectomy and modified Hinsberg operation on the labyrinth were therefore done. No fistula in the bony labyrinth or in the fallopian canal was observed, nor was pus encountered on opening the external semicircular canal or upon removal of the stapes. However, when the promontory was uncapped frank purulent exudate and granulations were seen on its inner aspect. A modified Panse flap of the skin of the external auditory canal completed the procedure. Sulfadiazine, now administered by mouth, was continued after operation, which was followed by an uneventful recovery.

When reexamined (in the Out-Patient Department), upon his discharge from the hospital, it was found that the middle ear and mastoid cavity had completely epithelialized and were dry throughout; the facial nerve had regained practically complete function.

COMMENT

On admission to the hospital the patient presented signs and symptoms which were highly suggestive of acute mastoiditis. The presence of the facial paralysis in itself was not the deciding factor for or against operation, but the time of onset of the paralysis in the course of an otitis was important in evaluating the indications for operation. As it is well known, involvement of the facial nerve at the outset of otitis media does not have the same significance as it does when it appears late in the disease. The facial paralysis occurred at the end of 12 days of the otitis during which there was ample time for the development of bone necrosis in the fallopian canal. However, the history of a previous facial paresis (on the opposite side 19 years earlier) occurring in association with an otitis media which resolved spontaneously was one of the deterring factors for immediate operation on the recently affected (left) side. Therefore, a period of observation from 24 to 36 hours was decided upon.

The finding at the original mastoid operation of a collection of purulent exudate in close proximity to the fallopian canal even though the latter appeared

grossly intact, was deemed sufficient evidence that this was the probable site of involvement of the facial nerve.

The sudden and simultaneous onset of labyrinthine and meningeal signs in the course of a middle ear infection is unusual. While it is not uncommon for a labyrinthitis to be complicated by meningitis, the latter usually occurs after an interval of days or weeks.

There has always been unanimity of opinion that labyrinthine disease in the presence of evidence of extension to the intracranial contents calls for immediate operative intervention upon the labyrinth. Nevertheless, in this case the meningitis was so fulminating and the risk of operation was considered so grave that it was decided to treat the meningitis first, temporarily deferring operation until the administration of a full course of chemotherapy could be completed. This decision was shown to be fully justified by the fact that the meningeal signs and symptoms had improved remarkably in the short period of time (24 to 36 hours). The patient was then in much better physical condition to withstand the radical mastoidectomy and labyrinthine operation, as shown by subsequent events.

The management of this case is in full accord with the present attitude taken towards cases of thrombosis of the lateral sinus. Even prior to the advent of chemotherapy we had learned to appreciate the value of deferring operation on the sigmoid sinus at the height of the febrile state, or during a chill, and of proceeding with the operation when these symptoms have subsided, usually after a period of from 2 to 6 hours. We have had no cause thus far to regret this course.

Now, a very pertinent question may be asked with regard to the case under discussion: since the meningitis had apparently been satisfactorily controlled by chemotherapy, was subsequent operation upon the labyrinth necessary; could not the suppurative process within the labyrinth have been similarly affected by the sulfadiazine? While it is felt that the latter part of the question can be properly answered in the affirmative, the risk taken in not operating or in undue delay in operating was far too hazardous. This opinion is based on the fact that chemotherapeutic agents may temporarily check an infection within the temporal bone only to be reactivated sometime after the administration of the drug was discontinued. A latent suppurative process locked up in a more or less closed space, as is the case in the labyrinth, may suddenly light up after weeks or even months and extend to the adjacent intracranial structure, the cerebellum, resulting in abscess formation, a condition which does not usually respond satisfactorily to chemotherapy.

LIFE'S LATER YEARS

STUDIES IN THE MEDICAL HISTORY OF OLD AGE

FREDERIC D. ZEMAN, M.D.

[New York City]

PART 6¹

THE MEDICINE OF ISLAM

(732-1096 A.D.)

"Looking back from the vantage point of A.D. 1925 we are tempted to look upon the Middle Ages as one of ignorance, superstition, bigotry and lawlessness, while fighting and religion occupied the whole attention of the great men of these ages; and standing amid the great leaders of the misty past, we see the great figures looking down upon us from the visor of the knight and the cowl of the monk; but the Arabist tradition of Mediaeval Europe brings to our minds yet another great figure, that of the Arab physician-philosopher and his gold and silver brocaded turban and his halo of intellectual curiosity and broad tolerance, and who are they amongst us who would place him among the least of these?"

D. Campbell—Arabian Medicine.

The manifold contributions of the Moslem world to our culture are well known. The fascinating tale of the preservation of Greek philosophy and science in the shape of Arabic translations is familiar to all students of history. At a time when western Europe found itself in intellectual darkness, the Caliphs of Bagdad and Cordova were actively encouraging the study of the Greek texts and the application of their lessons to the practice of medicine in hospitals founded by them. The success of these efforts is to be seen in many Arabic manuscripts that have come down to us, making known the thoughts of the great medical men, whose opinions, of much weight in their own day, were later to be enshrined as the authoritative word in medicine for many centuries.

The Arab physicians have been accused of many sins, and often with justice. Under their influence surgery languished; they encouraged unquestioning respect for authority; they indulged in over-elaborate classifications and delighted in hairsplitting discussions. They frequently misinterpreted their idol Galen, and thereby caused worse confusion. On the other hand they did preserve the Greek texts, even if at times in garbled form; they contributed excellent descriptions of disease, as seen at the bedside; they devoted great study to therapeutics in general and especially to dietetics; they contributed many new drugs and endeavored to study their action, and finally, raised the position of the healer to

¹ This is the sixth in a series of articles dealing with Studies in the Medical History of Old Age. Upon completion of their publication, the installments will be collected and reprinted in a single volume, constituting the third in the Series of Monographs of The Mount Sinia Hospital Press.—Ed.

the dignity of a learned profession. Their contributions to the medical study of old age are particularly noteworthy. They include discussion of the nature of aging, the differences between old age and youth, the proper regimen for the old, and the peculiarities of disease in the aged. One Ibn al Haitham or Alhazan (996-1038) of Bassora, according to Garrison, published a *Thesaurus of Optics* (Basel 1572) which contains the first note of ocular refraction and of the fact that a segment of a glass ball will magnify objects. The interest of the great Arab writers in the problems of advanced age is directly reflected in the works of later writers, such as the eminent Roger Bacon (1210-1292) and Arnold of Villanova (1235-1312), whose consulting practice covered France, Italy and Spain.

The Eastern Caliphate, with its center at Bagdad, produced three renowned figures, Rhazes (860-932), Haly Abbas (d. 994) and Avicenna (980-1037). The latter was truly a universal genius, for he not only wrote many volumes on medical subjects, but also contributed to geology an epoch-making description of the origin of mountains. He is said to have been a convivial spirit, enjoying life to the full, and meeting an early end as the result of excesses. One group of scholars attributes to him the authorship of the celebrated poem ascribed to Omar Khayam, and known to us in Fitzgerald's magnificent rendition. But Avicenna's greatest work was the *Canon*, described by Garrison, as "a huge unwieldy storehouse of learning, in which the author attempts to codify the whole medical knowledge of his time and to square its facts with the systems of Galen and Aristotle." Gruner (2) has provided a translation of the first book of the *Canon*, and here we find abundant references to old age.

"There are four periods of life:—

1—The period of growth,—adolescence—up to 30 years.

2—The prime of life,—period of beauty—up to 35 or 40.

3—Elderly life,—period of decline—senescence—up to about 60.

4—Decrepit age,—senility—to the end of life.

In the fourth period, the best vigor has passed, and the intellectual vigor begins to decline."

"To sum up, the equable temperament of the period of juvenility and youth is hot, whereas that of the last two periods is cold. The body in juvenility is additionally of a moist (equable) temperament, in that growth is proceeding; the moistness is shown by the softness of their bones, nerves and other members, and by the fact that at this age it is not going to be long before the semen and ether will come to manifestation. Old persons and those in the decrepit age are not only colder but drier in temperament. This is evidenced by the hardness of the bones, the roughness of their skin, and the long time which has elapsed since they produced semen, blood and the vapor (ether) breath."

"In summertime the humors are dispersed; the faculties and natural functions are impaired due to the excessive dispersion. The blood and

serous humor are diminished in amount; the bilious atrabilious humor increases in amount as a result of the dispersion of attenuated matters, whereby the heavier particles stay behind in increasing amount. This is why old persons and those of similar nature feel stronger in summer.

The first part of autumn is to some extent beneficial to old people, but the last part is very injurious to them. (In the first place there is the cold, in the second place there is the residue of the oxidation of humors of summertime.)

Winter is inimical to old persons and to those akin to them in nature. Middle aged persons are likely to be in health."

The effect of age and sex on the pulse:—

"Elderly persons,—The pulse is here smaller because of the weakness of the vital power; the swiftness is lessened both because of this and because of the lessened resistance. Such a pulse is therefore more sluggish.

Old age,—In the advanced years of life, the pulse becomes small, sluggish, slow. If it be also soft this is because of extraneous, and not natural humors."

Variations of the urine according to age:—

"Infancy,—The urine tends to the character of milk, considering the food and their moist temperament. Hence it is nearly colorless.

Childhood,—The urine thicker and coarser than in adolescents, and more turbid. This has already been mentioned.

Adolescence,—The urine tends to igneity, and to homogeneity.

Later life,—The urine tends to be white and tenuous but it may be coarse ("thick") because of the effete matters which are now being evacuated to a greater extent by way of the urine.

Decrepit age,—The urine whiter and still more tenuous. A similar coarseness to the proceeding may develop but this is rare. If the urine becomes very thick it intimates liability to develop calculus."

Following the detailed description of the manifestations at different times of life, we find an entire chapter devoted to "General Remarks on the Regimen of Old Age." The opening paragraph indicates how the treatment of the old proceeds logically from the observations on the "coldness" and "dryness" of the body at that time of life.

"In brief, the regimen appropriate for old people consists in giving those offerings of aliment, drink and baths which render the body warm and moist (i.e. moistening, calefacient food; warm or hot soft water baths). There should be plenty of sleep; and the time spent on the couch should be liberal; more than is legitimate for adults. The flow of urine should be continually assisted by diluents; the mucus should be helped out of the stomach by way of the bowels and urine. The nature is too soft and this needs correcting."

Then follows a detailed discussion of the food for the elderly. Judging by the frequency with which they are quoted these rules had wide influence on all later writers for several hundred years,—and is on the whole so rich in commonsense as to have validity even to-day, however antiquated the underlying reasons have become. The following paragraphs are typical:—

“Food should be given in small amounts at a time. There may be two or three meals a day; divided up according to the digestive power, and according to the general condition, whether robust or weakly. In the latter case, at the second or third hour they may partake of well-baked bread and honey. At the seventh hour after the bath they may partake of some one or another of the foods we shall name later, which are laxative in action. At bedtime some laudable nutriment may be allowed.

When they are robust, old persons may have a rather more liberal supper as long as they avoid any gross aliment which is likely to give rise to atrabilious or serous humour, and avoid all hot, sharp, or desiccative foods, such as dishes made with vinegar, salt or hot aromatics, seasoning, pickles, etc. These may, however, be allowed as medicaments.”

Following Galen, stress is laid on its value for those “who like and can digest milk.” Asses’ milk is recommended. The effect of food on the bowels is stressed and the importance of easy evacuations for the decrepit is emphasized. The kinds of wine best suited to the old are discussed. Exercise receives very detailed attention. The whole chapter is a carefully considered contribution to the physical hygiene of old age.

The Western Caliphate, with its capital at Cordova, is noted medically for Albucasis (1013–1106), Avenzoar (d. 1162), Averroes (1126–1198) and Maimonides (1136–1204). The latter, most famous of all the Jewish physicians who played such influential rôles in Moslem and medieval medicine, is known both for his religious and medical works. His “Guide to the Perplexed” attempted to reconcile the duties of the Jew to his faith and to the world in which he lived. While rejecting much orthodox tradition, he contributed biblical commentaries and legal elucidations to the Talmud. He is to be thought of as one who endeavored to bring about a fusion of Greek and Hebrew viewpoints, a task to which he brought an unusually independent mind.

In his “Aphorisms,” a book which attained great popularity, he dares to call attention to more than forty inconsistencies in Galen. This questioning of authority is unique in the medical literature of the time. Oddly enough one of the examples has to do with Galen’s saying in one place that body temperature is unaltered by age and in another saying that it decreases as a person grows older. Maimonides was much concerned with the significance of old age, especially in regard to treatment. In his “Treatise on Hemorrhoids” (3) he recommends incision in cases of thrombosed veins, but if the patient is too old, the application of dry cups to the lumbar region.

His “Book of Poisons” was written in 1199 at the request of his patron the Kadi al-Fadil, to avert the great danger of snake bites so prevalent in Egypt at



FIG. 1. Avicenna or Ibn Sina (980-1037), known as the "Prince of Physicians." (Reproduced from print in the collection of the Home for Aged and Infirm Hebrews, New York).



FIG. 2. Moses ben Maimon or Maimonides (1135-1204). A traditional portrait. (Reproduced from "Spanish Influence on Medical Science," Wellcome Foundation, Ltd., London, 1935).

the time. For internal poisoning as opposed to snake bite, he recommends the use of mandrake, bezoar, theriac and the like. With regard to the size of the dose, Maimonides tells us that this depends upon the intensity of the poison, the age of the patient, and the season of the year. He relates an interesting story in connection with this point. When he was a young man at Fez, there lived in that city a Vizier by the name of Ali ibn Yussuf. This man had reached the age of 120 years when he took seriously sick. Two doctors were called to his bedside, and they prescribed half a dram of theriac to be taken in the middle of the night. Just before dawn they came into his room and found him dead. The doctors looked solemnly at the body and gave two different opinions as to the cause of the Vizier's death. The first doctor said that the dose of theriac was too small, and the other that it was too large. A third doctor was called in and wisely decided that the Vizier had died not because of the medicine, but because of his old age (4).

Maimonides' writings are often popular in character, emphasizing rules of hygiene for his highly placed patrons at the court. He advised that convalescents and elderly people especially should consult their physicians frequently. He warned against over-indulgence in coition (5), particularly stressing the dangers to the aged and sufferers from heart disease. He believed in the moderate use of wine, as more conducive to health in older people than in younger ones and of special tonic value to the aged and enfeebled (6). He was an untiring foe of superstition and astrology.

The doubts expressed by Maimonides as to the credibility of Galen were slow in influencing medical thinking. The Arabization of Western Europe was due to the efforts at Salerno of Constantinus Africanus (c. 1020-1087), the translator into Latin of many of the Arab classics. This mode of thought achieved wide and unquestioned acceptance until the seventeenth century. We must remind ourselves that the great revival of learning, the Renaissance, was anticipated in the original thinking and the expression of honest doubts by many courageous men whose activities covered the centuries preceding.

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- [5] MEYERHOF, M.: *The Medical Work of Maimonides*, in *Essays on Maimonides*. N. Y., Columbia Univ. Press, 1941. Meyerhof points out that works such as the book on poisons and on sexual intercourse, belong to a well known type, popular with the princes and other prominent personages of that day. An Arabic bibliography lists several hundred such books written between the 9th and 13th centuries.
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MASSIVE PULMONARY EMBOLISM, V¹

BASED IN PART ON A STUDY OF EIGHTY-EIGHT FATAL CASES²

HAROLD NEUHOF, M.D., AND SAMUEL H. KLEIN, Major, M.C., A.U.S.³

ILLUSTRATIVE CASES (*continued*)

Case 29. Incision and drainage of abscess of foot. Sudden death in 10 minutes on the 11th postoperative day.

History: P. F. (Adm. #370697) was an obese woman aged 48 years. She was known to have had diabetes which was easily controlled by diet. She was admitted to the hospital for treatment of cellulitis of the left foot secondary to ulceration at the base of the second toe. Incision and drainage were performed under gas-oxygen-anesthesia. The postoperative course was entirely uneventful for 11½ days. Suddenly she was seized with severe pain in the chest, followed immediately by profound shock and profuse perspiration. She vomited four minutes later. Her pulse became imperceptible, there were severe dyspnea and cyanosis, and she died 10 minutes after the onset of symptoms.

Post mortem examination: The coronary vessels were negative.

There were six thrombotic masses, 5-10 cm. long, cylindrical in shape, and 5-7 mm. in diameter, located in the inferior vena cava below the auricular opening, the right auricle, right ventricle, pulmonary conus and artery and the main pulmonary artery branches (fig. 12). The thrombi had tapering ends, and in places were bifurcated. Many of the arteries deep in the parenchyma of the lung contained short coagulated dark-red masses. No thrombi were adherent.

Comment: This case is presented to illustrate the large number of massive emboli which apparently migrated simultaneously, and the extent of their distribution from the inferior vena cava through both chambers of the right heart, the pulmonary artery and its two main branches. The clinical picture presented by this patient consisted of a combination of severe chest pain, shock and asphyxia, with a rapidly fatal termination in 10 minutes.

Case 31. Right indirect inguinal hernia; dyskeratosis of left labium majus. Hernioplasty, excision of labium majus. Onset of cough on the 3rd postoperative day. Respiratory difficulty and cyanosis on the 5th day. Sudden collapse about 20 hours later, and death in 15 minutes.

History: B. S., (Adm. #350201), was a somewhat obese woman, aged 49 years. There were moderate varicosities on both lower extremities. Hernioplasty and excision of the labium majus were performed under gas-oxygen-ether anaesthesia. The postoperative

¹ This is the fifth installment of a series of seven articles dealing with the problem of Massive Pulmonary Embolism. Upon completion of their publication they will be collected and reprinted in a single volume, constituting the second in the Series of Monographs of the Mount Sinai Hospital Press.—Ed.

² From the Surgical and Medical Services and the Laboratories of The Mount Sinai Hospital.

³ Major Klein, adjunct surgeon to The Mount Sinai Hospital and now serving overseas with The Mount Sinai Hospital Unit, has contributed the study of the fatal cases and the analysis on which the work is based.

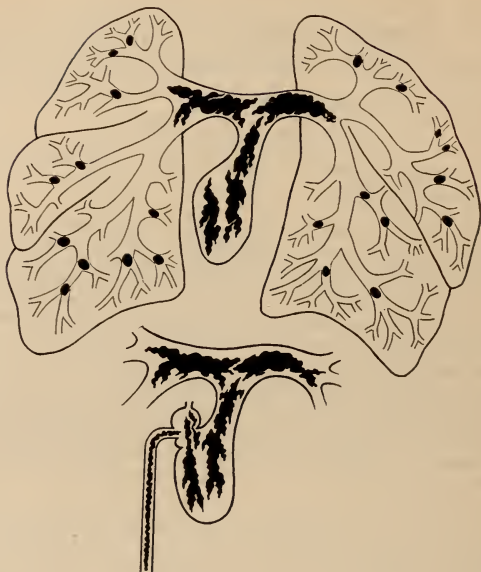


FIG. 12. Case 29



FIG. 13. Case 31

course was uneventful until the 3rd day, when the patient began to cough, and her temperature was 102.2°F. She was still coughing the next day. The following is an outline of the subsequent clinical course:

"2:55 A.M. Respiratory difficulty. Marked cyanosis.

5:00 A.M. General condition improved.

5:15 A.M. Patient stuporous about 5 minutes. Respirations more labored.

6:30 A.M. Patient now responds well. She is coughing occasionally, and there appears to be much mucus in her throat.

11:30 A.M. Patient dyspneic, orthopneic, and moderately cyanotic.

3:45 P.M. Heart sounds are of poor quality. Pulse is rapid (130 per minute); respirations 26 per minute. The clinical picture is that of cardiac embarrassment. The electrocardiogram shows only left ventricular preponderance and inversion of T3.

8:30 P.M. Pulse 122, respirations 26, temperature 100.6°F. Patient's color is good; there is now no cyanosis although her breathing is somewhat labored. Pulse is regular. Patient is alert and restless.

11:30 P.M. Patient suddenly in shock. Purple cyanosis present. She is gasping for breath; pulse is imperceptible; heart sounds faint and irregular. Adrenalin injected directly into the heart.

11:45 P.M. Patient died."

Post mortem examination: The coronary vessels were negative.

There was a large infarct in the right lower lobe, and small infarcts in the right upper and left lower lobes.

The branches of the pulmonary artery leading to the infarcts each contained an obliterating embolus firmly attached to the vessel wall. The outflow tract of the right ventricle contained three free, floating, firm, irregular, small cherry-sized thrombotic masses (fig. 13).

Comment: In this case, death was the result of a combination of 3 infarct-producing embolisms in the right upper and lower lobes and the left lower lobe respectively, and 3 cherry-sized emboli in the outflow tract of the right ventricle. The clinical picture was a composite of the features of asphyxia, cardiac embarrassment and cerebral anoxemia.

Case 45. A. M. (Adm. 349755). A 37-year old woman. *Progressively downhill clinical course for ten weeks, following exploratory laparotomy for papillary cystadenocarcinoma of the ovary with generalized intra-abdominal metastases.*

Post mortem findings: Beginning in the pulmonary artery and extending into the intrapulmonic branches, there was a large, friable, mottled-red and gray thrombotic mass which was slightly adherent. It extended into the pulmonary artery branches down to those of 3-4 mm. diameter (fig. 14).

Comment: This case is presented to illustrate the occurrence of massive pulmonary embolism without localizing signs or symptoms in a patient undergoing slow progressive deterioration due to abdominal carcinoma.

Case 7. Acute appendicitis; pelvic peritonitis. Appendectomy, and drainage. Progressively unsatisfactory postoperative course. Phlebitis at sites of "cut-down" intravenous infusions. Patient died on the 9th day.

History: N. K., (Adm. #317010), was a young man, aged 22 years, who was operated upon for ruptured gangrenous appendicitis with pelvic peritonitis. Appendectomy was performed under spinal anaesthesia and the pelvis was drained. Postoperatively, he did poorly. His temperature was between 103°F. and 105°F. There was gastric retention and dilatation which required repeated lavage. Phlebitis occurred in the right ante-cubital fossa, then the left and the right ankles, the sites of "cut-down" intravenous infusions. On

the 9th day his condition became very poor. Then, without developing any physical signs in the lungs or any other localizing signs, he became cold and clammy and somewhat cyanotic, and died.



FIG. 14. Case 45



FIG. 15. Case 7

Post mortem examination: There was pelvic peritonitis.

The left external iliac vein was discolored on its outer surface, and was distended by a firm thrombus which was composed of two portions. One part was light yellow and had an irregular surface; the remainder was a continuation consisting of reddish clot.

There were scattered foci of bronchopneumonia and a few scattered infarcts in the right lower lobe and the left lung. A thrombus was found leading into a branch of the left pulmonary artery which continued by means of a reddish thrombus into the right ventricle (fig. 15).

Comment: This case is presented to illustrate preliminary pulmonary infarctions and terminal massive embolism without clinical manifestations to indicate their presence.

Case 36. Chronic lupus erythematosus; atypical verrucous endocarditis. Episodes of phlebitis over a period of 1½ years. Death after a septic course of one month.

History: M. G., (Adm. #375071), was a girl, aged 26 years, who had been ill with chronic lupus erythematosus for three years. One and one-half years prior to admission she had been confined to bed for three months with left femoral phlebitis which occurred after an abrasion of the knee. It was followed by chronic edema of the left leg. When the patient was admitted to the hospital, she presented pitting edema of both ankles, more marked on the left. The edema disappeared with rest in bed. During the second week of her hospital stay, she developed phlebitis of the right brachial vein at the site of an intravenous infu-



FIG. 16. Case 36

sion. One week later, there was a deep phlebitis of the right calf associated with edema of the ankle.

In the fourth week, she had an upper respiratory infection with cervical adenitis. Soon after, she had a chill, became cyanotic, and the temperature curve became septic in nature. The lungs were negative on physical examination. Three days later, a blood culture was positive for streptococcus viridans. On the following day she had another chill, there appeared signs of peripheral circulatory collapse, respiratory failure and air hunger, and the patient died just as a blood transfusion was begun.

Post mortem examination: Chronic adhesive pericarditis. Atypical verrucous endocarditis (right ventricle and tricuspid valves).

There was an infarct in the lower portion of the right upper lobe.

The pulmonary artery was free. The main branches of both pulmonary arteries were completely occluded by firm grayish-yellow masses which were adherent to the vessel wall. In some of the branches the occluding thrombi could be traced peripherally from these masses for a considerable distance (fig. 16).

The left femoral vein, just below the inguinal ligament, was completely occluded by an adherent reddish thrombotic mass. Tracing the veins farther up, there was in the left

common iliae vein, pink granular material which was rather intimately adherent to the wall and almost completely filled the lumen. This mass was 2 cm. in length. The corresponding level of the right common iliae vein appeared slightly granular and at this site a granular clot was found free in its lumen.

Comment: This case also illustrates unsuspected infarction and occluding massive pulmonary embolism in a critically ill patient. That the emboli had been in the pulmonary arteries for some time is demonstrated by their complete adherence to the intimal lining of the vessels.

Case 9. Thrombo-angiitis obliterans; coronary artery disease; myocardial insufficiency. Acute collapse and death in 15 minutes.

History: I. T., (Adm. #333212), was a well-developed and well nourished man, aged 45 years. He had had intermittent claudication for 6 years, and had had gangrene of the right little toe which necessitated amputation. The diagnosis was thrombo-angiitis obliterans. For 8 months he had been troubled with attacks of preordial constriction and pain radiat-



FIG. 17. Case 9

ing down the left arm, associated with dyspnea, profuse perspiration, pallor, and sensation of impending death.

Two weeks prior to admission, he developed signs and symptoms of myocardial insufficiency which responded promptly to treatment. The electrocardiogram indicated intra-ventricular conduction defect.

He was soon well enough to be out of bed. One afternoon, he suddenly developed one of his attacks of paroxysmal dyspnea; he became cyanotic and pulseless and lapsed into coma. He ceased breathing 15 minutes later. It was noted that several respirations occurred after the heart stopped beating. The clinical diagnosis was "fresh coronary thrombosis."

Post mortem findings: There was myocardial fibrosis of the lower half of the interventricular septum. The coronary arteries were patent throughout. The left circumflex coronary artery and the anterior descending ramus were thickened and narrowed.

In the right iliae vein there were two valves which contained adherent dark red blood clot. In the region superior to this for about 2 cm. the intima was dark red, dull and roughened, suggesting phlebitis.

The pulmonary conus and both pulmonary arteries contained soft, dark grayish-red non-adherent embolic masses (fig. 17). In both pulmonary arteries and in the smaller branches

particularly near the bifurcations, there were small adherent pinkish white masses 5-10 mm. in diameter, probably representing older organizing emboli. Microscopic examination revealed a number of pulmonary arteries showing complete organization of thrombi with marked narrowing of the lumen. Sections of the pulmonary thrombi showed areas of hyalinization with organization, fibrosis and canalization.

Comment. The fatal episode in this patient consisted of dyspnea, cyanosis, coma and cardiac failure following a massive pulmonary embolism. An interesting feature in this case is the fact that several respirations occurred after the heart had stopped beating, which would seem to indicate that cardiac failure was the essential mechanism of death, respiratory failure occurring secondarily.

It should also be noted that there were organizing emboli, 5-10 mm. in diameter in the smaller branches of the pulmonary artery, without, however, any evidence of infarction of the lungs.

Case 65. Hypertrophied prostate; pycelonephritis. Bilateral vas deferens ligation. Sudden onset of tachycardia, dyspnea and cyanosis on the 13th day, followed by improvement. Death in ten minutes five days later.

History: H. K., (Adm. #413178), was a thin male, aged 72 years, who was admitted to the hospital with urinary retention of five days' duration. He was operated upon, following vesical decompression, two days after admission. Bilateral vas deferens ligation was performed under local anaesthesia, as a preliminary to prostatic resection. Postoperatively there was fever up to 103 F., tenderness in the right costo-vertebral angle and positive blood culture for B. Coli. After several days he began to improve, and the blood culture became negative. On the 13th days, the pulse rose abruptly to 160 per minute, with irregular rhythm due to dropped beats. Coincidentally, dyspnea and cyanosis appeared. The clinical impression was "acute coronary thrombosis." The electrocardiogram, however, revealed only auricular paroxysmal tachycardia. The symptoms and physical signs cleared up after several hours, but two days later, dyspnea and cyanosis again appeared, the sputum was slightly rusty, and there were physical signs of pneumonia of the right lower lobe. The patient again improved for several days. However, on the 18th postoperative day, his respirations suddenly ceased, although the heart action remained strong for ten minutes, and then stopped.

Post mortem findings: There was an organizing infarct, 2 x 4 cm., in the right lower lobe.

The pulmonary artery and both the right and left main branches contained massive emboli, which were yellow and red and were 0.8 cm. in diameter. The emboli started in the right ventricle, partially filled the lumen of the pulmonary artery and one was folded upon itself at the bifurcation. It extended 2 cm. into the left branch and could be traced through the right main branch into the branch to the right lower lobe, which was completely occluded. The clot was not adherent at any point (fig. 18).

Comment: In this case, the fatal episode was ushered in by sudden cessation of respiration; the heart continued to beat for 10 minutes thereafter. The mechanism of death appears to have been respiratory failure, possibly reflex in nature, with secondary cardiac stoppage.

The next two cases are presented to illustrate the occurrence of acute structural changes in the myocardium following pulmonary embolism. Both cases have previously been reported by Horn, Dack and Friedberg (81), to whom we are indebted for permission to report their histological findings.

Case 42. Carcinoma of the descending colon. Caccostomy. Death in 10 minutes on the eighth postoperative day.

History: B. D., (Adm. #414180), was an obese woman, aged 58 years. Exploratory laparotomy was performed under spinal anaesthesia; hepatic and omental metastases were



FIG. 18. Case 65

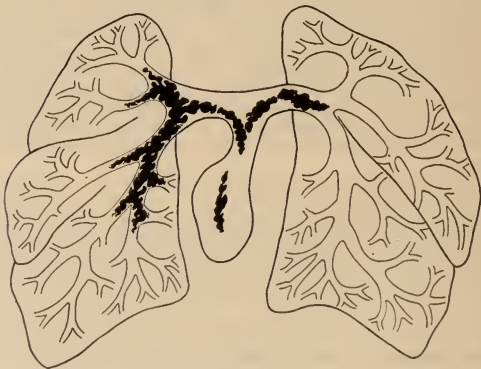


FIG. 19. Case 42

found; caccostomy was performed. The postoperative course was satisfactory. On the second day it was noted that, for a short time, the patient had some difficulty in breathing. However, her condition was good until early on the morning of the eighth day, when she suddenly began to breathe stertorously and became slightly cyanotic. The respirations became slow and deep, the pupils were in mid-dilatation, and the tongue was deviated to the left. The deep reflexes could not be elicited. The heart sounds were of fair quality and the

cardiac rate was somewhat accelerated. The patient died 10 minutes after the onset of these symptoms. It was noted that the pulse continued to be palpable for a few moments after the respirations ceased. The clinical impression was "cerebral accident or pulmonary embolism".

Post mortem findings: Lying in the right ventricle and extending into the pulmonary artery were several fragments of inelastic grayish-red blood clot which were cylindrical in shape. These clots were considerably smaller than the caliber of the pulmonary artery. The largest piece had a maximum diameter of 1.5 cm. and a length of 7 cm. The blood clots extended into both main branches. In one of these, "currant jelly" clot continued from a thrombus into the smaller pulmonary artery branches (fig. 19).

The coronary vessels and ostia were patent throughout. Their walls showed only a moderate number of flat, intimal arteriosclerotic plaques.

The following are the microscopic findings in the heart muscle as noted by Horn, Dack and Friedberg (81): "Histologic examination of the septum revealed scattered foci of fatty change and glycogen. There were several localized areas of necrosis, with early cellular response of polymorphonuclear leukocytes and lymphocytes. These foci were situated chiefly in the subendocardial zones. There were also patches of edematous and young (cellular) connective tissue. Within the right ventricle were slightly patchy cellular zones of connective tissue."

Comment: Acute cardiac damage was observed microscopically in this case without any noteworthy concomitant coronary disease.

The mechanism of the production of myocardial alterations secondary to pulmonary embolism will be discussed later.

Case 67. Coronary artery disease. Clinical picture of "congestive" heart failure and pulmonary infarction. Sudden collapse and death in 17 minutes.

History: B. E. (Adm. #413096), was an obese man, aged 44 years, who came to the hospital complaining of dyspnea on exertion for one year. Three days before admission, he experienced sudden pain along the costal margin posteriorly, aggravated by respiration and associated with dyspnea. The pain subsided in about an hour, but recurred two days later. Cough appeared, productive of blood-tinged sputum. Examination on admission revealed cyanosis, and dullness over the right lung base. The electrocardiogram: regular sinus rhythm, left axis deviation, a deep S1 and a deep Q3. The QRS complex was M-shaped in lead II. T3 was inverted. X-ray examination of the chest indicated the presence of pneumonia of the left lower lobe. The clinical impression was "congestive heart failure; pulmonary infarction." The patient's condition remained fair. Occasionally, he brought up some bloody sputum. Ten days after admission, he suddenly complained of severe precordial oppression and air hunger and he rapidly became very cyanotic and restless. His breathing became gasping in character, the heart sounds became weak, and he died 17 minutes after the onset of the acute collapse. In view of the previous pulmonary infarction, the cause of death was considered to be a massive pulmonary embolism.

Post mortem findings: There were multiple infarcts in the right lower lobe. The right auricle was dilated and contained two free, cylindrical, gray-red, granular friable masses which measured 1.5 x 3 x 2 cm. There was a similar thrombotic mass in the left trunk of the pulmonary artery which occluded the lumen. This mass extended part way into the right pulmonary artery, and was propagated as dark-red (post-mortem?) clot into the right upper and middle lobe branches. None of these clots was adherent. However, a similar occluding mass in the right lower lobe branch of the pulmonary artery was partially adherent (fig. 20).

Horn, Dack and Friedberg (79) reported their microscopic findings in the heart muscle of this patient as follows: "The myocardium of the posterior wall of the left ventricle showed an extensive, stellate, gray-white, firm, fibrous zone. The coronary ostiums were

patent. There was widespread sclerosis of the coronary arteries, especially of the right, with moderate narrowing of the lumens.

Histologic examination of various portions of the left ventricle revealed focal areas of myomalacia, with subendocardial hemorrhage, vacuolar degeneration of the myofibrils, scattered proliferation of mesenchymal cells and occasional wide zones of interstitial polymorphonuclear leukocytes. There was also evidence of patchy fibrosis and a moderate degree of fatty change. Sections through the right ventricle showed evidence of myodegeneration, with an occasional polymorphonuclear leukocytic reaction."

Comment: According to Horn et al., the electrocardiographic changes were those accepted as common in cases of pulmonary artery embolism but in this case might more probably have been due to an organized infarct of the posterior wall of the left ventricle. At necropsy, acute myocardial changes were found which could not be accounted for by any recent coronary artery occlusion.

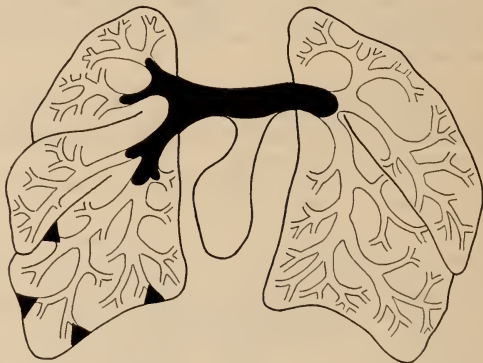


FIG. 20. Case 67

Case 68. Lobar pneumonia. Clinical course satisfactory. Subsidence of the pneumonia. Sudden onset of shock on the 12th day, followed by improvement after one day. Sudden collapse and death in one and one-half hours three weeks later.

History: H. P., (Adm. #277320), was a well developed and well nourished man, aged 62 years, who was admitted to the hospital with right lower lobar pneumonia of five days' duration. Four days later his temperature was normal, his general condition much improved and the x-ray examination revealed resolving pneumonia in the right lower lobe. He was soon well enough to be out of bed. On the 12th day after admission, he suddenly went into shock. He improved after a few hours, but the next day was again in very poor condition. He was very cyanotic, cold and clammy, with weak heart sounds and rapid respirations. However, he again improved and made a good recovery. Three weeks later he suddenly became dyspneic and complained of precordial pain. His pulse was rapid but of fair quality, and his skin was cold. He lapsed into unconsciousness after about an hour and twenty minutes and died fifteen minutes later.

Post mortem findings: The veins of the legs were noted to be distended and nodules could be felt along their course.

There were two large autolyzing infarcts in the right lower lobe, and there was an organized embolus in the artery supplying this area. There were also fresher lightly adherent emboli in other branches of the pulmonary artery, and some branches contained recanalized thrombi (fig. 21).

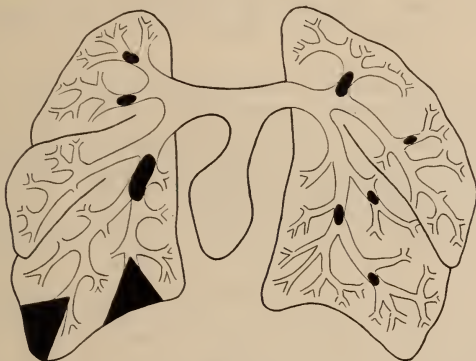


FIG. 21. Case 68

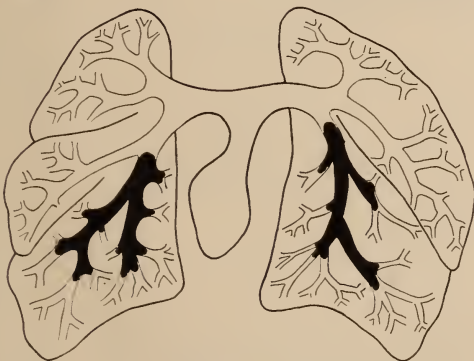


FIG. 22. Case 78

Comment: The acute severe reaction following the initial infarctions in the right lower lobe on the 12th hospital day illustrates that the clinical picture, due to a relatively minor embolism, may be indistinguishable from that produced by massive embolism of the major pulmonary vessels.

A rapidly fatal episode occurred three weeks later following secondary embolism of other pulmonary arterial branches.

It should be noted that death was caused by peripheral embolisms in this case; the main pulmonary arteries were not involved.

Case 78. Chronic cholecystitis and cholelithiasis. Cholecystectomy. Postoperative course uneventful until the 9th day. Sudden collapse and death in 10 minutes.

History: B. T., (Adm. #302985), was an obese woman, aged 54 years. Operation was performed under spinal anaesthesia. The postoperative course proceeded without untoward incident until the 9th day, when suddenly the patient's condition changed. She became cold and clammy, cyanotic and dyspneic, and her skin became peculiarly mottled. The heart sounds became inaudible. The patient lapsed into coma, her pupils dilated, she was incontinent, and died 10 minutes after the onset of the acute collapse. The clinical impression of the cause of death was pulmonary embolism.

Post mortem findings: The left leg was larger than the right. Both the right and left branches of the pulmonary artery to the lower lobes were filled with thrombotic masses (fig. 22).

Comment: In this patient, the terminal episode was characteristic of massive pulmonary embolism with obstruction of the main pulmonary arteries. The clinical picture was a combination of asphyxia, syncope and shock. However, the post-mortem examination revealed that the obstruction was incomplete, the emboli being found only in the branches of the pulmonary arteries to the lower lobes. This incomplete obstruction, nevertheless, was sufficient to produce a rapidly fatal terminal episode.

To be continued

ESSAYS ON THE BIOLOGY OF DISEASE¹

ELI MOSCHCOWITZ, M.D.

CHAPTER 8

OBESITY

"Leave gormandizing; know the grave doth gape
For Thee thrice wider than for other men"

Shakespeare, Henry VIII.

In this discussion, we shall not enter into the much debated causes of obesity because the ultimate effects are to a large extent independent of the cause.

Life expectancy in obesity. Dublin and Lotka (1) analyzed the duration of life in close to 200,000 men aged 21 and over according to weight. The following tables tell the story.

From these tables it is obvious that obesity shortens life proportionately to weight and age. The figures also imply that the longer the duration of the obesity, the worse is the life outlook.

TABLE I

Influence of weight in mortality: deaths per 100,000 men accepted for insurance

WEIGHT	DEATH
Standard.....	844
Underweight total.....	848
Overweight total.....	1111
Overweight 5-14%.....	1027
Overweight 15-24%.....	1215
Overweight 25%.....	1472

TABLE II

Influence of weight in mortality, as modified by age
Deaths per 100,000

WEIGHT	AGE (YEARS)	
	Under 45	Over 45
Standard.....	463	1308
Underweight, total.....	498	1274
Overweight.....	527	1824

¹ This is the eighth in a series of essays by Dr. Eli Moschcowitz in which an attempt is made to interpret certain forms of chronic disease from the biologic viewpoint as opposed to the current trend toward rigid classification implying a concept of disease as a more or less static phenomenon.

According to present plans these essays will appear in consecutive issues of the Journal of The Mount Sinai Hospital. When the publication of the projected series of essays is completed, the several installments will be assembled and printed in the form of a monograph.—Ed.

TABLE III
Influence of overweight on mortality in persons 45-50

POUNDS OVERWEIGHT	INCREASE IN DEATH RATE AVERAGE PER CENT
10	8
20	18
30	28
40	45
50	56
60	67
70	81
80	116

Relation of obesity to diabetes mellitus. The common association of obesity with diabetes is a well confirmed clinical observation. Joslin and his associates (2) report that among 1000 successive diabetics the maximum weight of only 8 per cent was below the standard, 15 per cent were in the normal zone and 77 per cent were above it. Between the ages of 51 and 60 there were only two diabetics in 252 whose maximum weights were below the normal zone prior to the onset of the disease. Among 2000 of their patients none occurred who was more than 30 per cent underweight. In all groups, there was a greater frequency in women. Moreover, actuarial statistics (Joslin, Dublin and Marks (3)) reveal that diabetes develops more frequently in obese individuals than in those of normal weight, and that the increase is proportionate to the weight. The mortality statistics parallel the impairment statistics. Inasmuch as diabetes mellitus is insidious in onset one would expect that a prediabetic state would be found in some instances of obesity and testimony is abundant that it does occur frequently as determined by a glucose tolerance test. Berlec and Fitz (4) in 32 cases of obesity found that a considerable number had typical diabetic curves. John (5) found a diabetic curve in 65 per cent with a high renal threshold (above 180 mgm. per 100 cc.), in 46 per cent, Embleton (6) found high glucose tolerance curves in 73 per cent of male obese patients and in 35 per cent females but up to the age of 35, high tolerance curves were noted in only 27 per cent of the males and in 23 per cent of the females. He did not find that the per cent of high glucose tolerance curves increases paripassu with the increase in weight. Short and Johnson (7) report that there was an unmistakable correlation between the degree of the overweight and the incidence of impaired glucose tolerance, irrespective of age.

The large incidence of high tolerance curves in obesity is only of significance when the time factor is taken into consideration, for such curves obviously do not spring up over night. Age alone has an effect on the incidence of impaired tolerance [Bertram (8), Marshall (9), Spence (10)]. Spence found a progressively higher glucose tolerance test from the third year of age on. John (11) in comparing the glucose tolerance curve of children and adults found that 82 per cent of children had normal curves, and 62 per cent adults. Short and Johnson found that age has a slight effect on the incidence of impaired tolerance; this was most noticeable from the 7th decade onward.

Under these circumstances the effect of obesity would have an added significance not only in relation to age, but also in regard to the duration of the obesity. Ogilvie's (12) study is particularly impressive in this regard. When sugar tolerance tests were plotted according to the duration of the obesity, he found that during the first 5 years of obesity, one-third of his patients showed an increased tolerance for sugar. After this period, the tolerance lies within normal limits up to the eleventh year of the obesity. After this year, diminished tolerance makes its appearance and after 18 years of obesity, every case shows a lowered tolerance and diabetes appears. Short and Johnson also think it probable that the duration of overweight determines the incidence of impaired tolerance. They hold that the two factors, age plus the degree of overweight accentuate the incidence of diminished sugar tolerance. In accordance with this evolution, Ogilvie (13) found hypertrophy of the islands of Langerhans in 13 of 19 subjects with obesity, most of them 49 years of age and upward, which he believes is compensatory for the excessive carbohydrate intake that so frequently initiates and continues the obesity. Inasmuch as no other study is available in reference to the hypertrophy of the islands of Langerhans in the early or prediabetic phase of obesity, Ogilvie's observations await confirmation but in this connection the finding of hypertrophied islands in babies of diabetic mothers is suggestive, [Gray and Feemster (14)], [Gordon (15) 4 of 4 infants], [Warren (16) 6 of 9 infants], [Helwig (17) 4 of 9 infants], [Potter, Seckel and Stryker (18) 2 of 4 infants], especially as most of these babies were overweight. The percentage of incidence is too high to be a matter of mere chance. That the hypertrophy is not specific is proven by their occasional presence in infants of non-diabetic mothers. Both Helwig and Potter and his associates found no correlation between the blood sugar and the morbid changes. The hypertrophy of the islands in association with the usual excessive weight of the infants suggest, as Ogilvie and Helwig assert, that the mechanism is a compensatory one, to meet the growth stimulus engendered by the hyperglycemia of the mother.

Additionally corroborative in this respect is the occasional occurrence of symptoms of hyperinsulinism in cases of obesity. I have recently seen two cases. Harris (19) probably refers to it under the term "dysinsulinism" and Conn (20) as "essential hyperinsulinism." Conn describes an illustrative case in a young obese girl whose fasting blood sugar was normal. This in his experience, differentiates it from hyperinsulinism of organic origin, wherein the fasting blood sugar falls to hypoglycemic levels by provocative methods. Essential hyperinsulinism according to Conn's view represents an exaggeration of the normal insulinogenic effect in healthy individuals who partake of a high carbohydrate diet. This observation is substantiated by the work of Horst, Ridout and Best (21) who found that animals deprived of food for 7 days have much less insulin in the pancreas than well fed animals.² At all events, a vicious circle is established and the sequence of events may be described as follows. As a result of

² Soskin (22) holds that the hypoglycemia curve following excessive carbohydrate ingestion is not due to insulinogenesis but to the fact that the liver fails to pour glycogen into the blood under the influence of a high carbohydrate intake. His views while provocative have not been widely accepted.

a high calory diet due to whatever cause, there is a compensatory overstimulation of the insular tissue. This induces a further craving of carbohydrates to satisfy the hunger, which again adds to the weight and so on. Whether eventually exhaustion of the insular apparatus results and diabetes develops in all instances will not be known until patients with essential hyperinsulinism have been followed over a long period of years.

Particularly suggestive in this connection is the experimental production of diabetes by anterior pituitary extract. Anselmino, Herold and Hoffman (23) found that the administration of anterior pituitary extract to normal rats resulted in substantial hyperplasia in the islands of Langerhans. They ascribe this increase to the action of a "pancreatotropic hormone" in the pituitary gland. Simultaneously they found an increase in the amount of insulin in the blood. Richardson and Young (24) found in rats by quantitative determination that the amount of islet tissue in animals that received daily injections of anterior pituitary extract for some weeks was double that of control animals. Marks and Young (25) found that the insulin content of the pancreas of the pituitary treated rat may be twice that of control animals suggesting that the extra islet tissue formed as the result of the hypophyseal stimulus is functionally active. On the other hand, in animals made permanently diabetic by anterior pituitary extract, the islands showed changes varying between depletion of the cytoplasmic granules of the beta cells (hydropic degeneration) to complete replacement by hyaline substance. This is the theory suggested by Falta (26) and it seems attractive because it accords with such available data that strongly indicate such a biological evolution. Moreover, there are other analogies in clinical medicine where hyperactivity passes into hypofunction, for instance, the occasional development of hypothyroidism after a long continued hyperthyroidism. But the problem of the relationship of obesity to diabetes will never be solved until systematic morphological and functional studies are conducted throughout the entire life cycle of the disease.

Obviously, in this discussion we must remember that the glucose tolerance test does not exclusively represent the function of the insular apparatus of the pancreas. Furthermore, the glucose tolerance test is modified by the previous diet of the patient (Conn), by the alkaline reserve and by other associated conditions. In any event, the glucose tolerance test is the best means at our command to determine a prediabetic state. One must also remember that when a prolonged and marked hypertension complicates obesity, the threshold for glucose rises sometimes to a considerable degree, as the direct consequence of the hypertension. Most hypertensives may therefore be regarded as potential diabetics. This factor modifies the incidence of diabetes in obesity to a considerable extent.

Recently, Newburgh and Conn (27) reported a series of overweight individuals, usually over 30 years of age, with spontaneous glycosuria and a high tolerance curve who were made sugar free by merely inducing a reduction in weight. They do not become hyperglycemic and the glucose tolerance curve becomes normal on a maintenance diet of 300 gms. carbohydrate provided they do not gain weight. Ninety per cent of such patients follow this rule, the other ten per cent do not.

A recurrence of the obesity reproduces the original picture. They suggest that this syndrome is due to the excessive accumulation of fat in the liver with a resulting impairment in the ability to accumulate glycogen at the normal rate. It is highly doubtful whether this syndrome is a distinct entity, nor can one say that these patients are "cured" because their glucose tolerance curve is normal and they have no glycosuria. The probability is strong that these patients represent a stage in the evolution of a true diabetes, and a long follow-up is highly essential to determine the ultimate fate of such patients.

It is very apparent that the diabetes that follows obesity is a matter of slow development, conditioned by many factors amongst others, heredity, and it is difficult to gauge, as in so many of the hyperkinetic diseases (28), when the transition from health to disease has occurred.

The relation of obesity to hypertension. Even in individuals within the range of normal weight, the blood pressure is in general proportionate to weight. Thus Alvarez and Stanley (29) found in prisoners that weight tends to increase the pressure after the age of 35. Even in normal children, Michael (30) found a correlation between systolic pressure and weight and height. In soldiers, Huber (31) found that hypertension is closely correlated with weight above the standard. Dublin, Fisk and Kopf (32) found a higher percentage of hypertension (20 mm. Hg. or more above a normal blood pressure for age) in overweight persons, than in those of normal weight. This correlation was especially marked as age advanced. The following table is based on large actuarial statistics (33).

TABLE IV

PER CENT	AVERAGE BLOOD PRESSURE MM. Hg	
	Systolic	Diastolic
underweight (-)		
overweight (+)		
-35 to -26	117.7	77.0
-25 to -16	120.6	79.2
-15 to -6	122.4	80.8
-5 to +5	124.1	82.1
+6 to +15	126.1	83.7
+16 to +25	127.4	84.7
+26 to +50	127.8	84.8

Gager (34) found that 28.3 per cent of obese patients of all ages had hypertension against 16.4 per cent of the non-obese. Master and Oppenheimer (35) in a study of obesity found that 67 per cent showed a hypertension of 150 mm. Hg. or over and that the height of blood pressure was correlated with the weight and especially with age. Symonds (36) conclusions are identical. Terry (37) found 58 per cent of his obese patients hypertensive, averaging 176 to 96 mm. Hg. After reduction of the weight, the average blood pressure was 170 systolic and 95 diastolic; it is evident therefore that the diastolic pressure is more resistant to the reduction than the systolic. Short and Johnson (38) in a study of 2858

applicants for insurance found that overweight exerted a positive influence in causing an increased incidence of hypertension, and the difference in average blood pressure was greatest in the sixth decade. He found the incidence less than the other observers. The hypertensive effect of gaining weight is well illustrated in Cushing's syndrome.

It is evident therefore, that weight plus age is a conditioning influence upon the development of hypertension. As corroboration, one may cite the reduction in blood pressure that is usually attendant upon a loss of weight, as Terry observed. This is especially noticeable in the early or labile phase of hypertension. Indeed, I have seen a moderate hypertension return to normal pressure levels and remain so for many years, and the more pronounced the weight and the earlier it is treated, the greater the reduction in blood pressure that may be expected. Again the diastolic pressure, as Terry observed, is less influenced than the systolic. Even in individuals of normal weight the reduction of a few pounds sometimes influences the pressure considerably. One cannot divorce temperament in the development of hypertension in the overweight. As I tried to show in Chapter 2 (Biology of hypertension of the greater circulation) hypertension is more apt to occur in temperaments that may be described succinctly as the antithesis of the child in mental make up. They usually overeat and do not play or take much exercise, factors which contribute toward overweight. This type of individual, in my experience, is more subject to the development and the hastening of the tempo of hypertension than stout individuals who have the conventionally recognized happy, playful and childlike temperament.

The mechanism whereby overweight raises the blood pressure is not entirely clear. I suggest that it is a compensatory effect to meet the extra burden placed upon the heart which does not always keep pace in size and weight with the growth of the body [Hirsch (39), Smith and Willis (40)]. This might explain the reduction in blood pressure after losses of weight, and the notorious tendency to a low blood pressure in thin individuals. This mechanism may also serve as the explanation for the steady rise in blood pressure, both systolic and diastolic, (although both are within the normal range) in normal pregnancy. [For literature see Jensen (41).]

The observations of Wood and Cash (42) are also suggestive. In dogs made hypertensive, the systolic pressure rose with gains in weight and fell with weight loss. The diastolic pressure varied little.

It is important to appreciate that primarily obesity causes a hypertension of the greater circulation only. This is also true of the experimental hypertension produced by Goldblatt [Katz (43)]. Obesity produces hypertension of the pulmonary circuit only after left sided failure has been initiated. For the final phase in hypertension of the greater circulation, see Chapter 2.

The relation of obesity to cardiac disorders. Obesity may affect the heart function in other ways than through the intermediacy of hypertension. The "fatty" heart or the "beer drinkers" heart no longer possesses the significance attached to it by the older generation of clinicians. This is largely due to the introduction of instruments of precision to measure cardiac function. Nevertheless, "fatty

infiltration of the heart"³ to a limited degree affects cardiac function, sometimes profoundly.

Müller (44) found that under normal circumstances, the size of the heart increased proportionately to the weight, according to the following table.

TABLE V

WEIGHT IN KG.M.	RIGHT VENTRICLE	LEFT VENTRICLE	SEPTUM
Men			
30-40	40.4	75.7	54.7
40-50	47.1	84.5	63.2
50-60	55.6	103.4	73.9
60-70	61.6	120.0	84.1
70-80	66.1	131.3	90.5
Women			
30-40	28.9	52.9	40.0
40-50	37.7	66.8	50.4
50-60	41.9	79.9	57.5
60-70	49.7	92.7	65.9
70-80	56.5	97.4	75.7

Hirsch (39) many years ago, found that in obesity the heart does not increase in size commensurate with the growth of the body, which he believed accounted for the premature heart failure. Smith and Willius (40) in a study of heart failure in obesity arrived at the same conclusion. In a fourth of their cases of obesity without primary disease of the heart, the actual weight was less than the calculated weight. They found that many factors were involved in the production of failure in obesity, the most important being, first, the fatty infiltration of heart which often penetrates as far as the endocardium and which, as a rule, involves the right heart to a proportionately greater degree than the left; and second, the increased amount of work to be performed to satisfy the excess of tissue to be nourished and the increased metabolism of the patient. Smith and Willius report 9 cases, most of them dying in heart failure, in which primary evidence of disease was lacking. These patients had no hypertension or any previous hypertension, and all were very obese. These observations of Smith and Willius prove that hearts in the obese may occasionally fail in the absence of pathological changes.

As the result of the high diaphragm, the heart is displaced upward and acquires a more horizontal position with a rotation of the electrical axis. Fishberg (45) believes it plausible that this displacement contributes to the handicap.

Wiggers (46) suggests another factor that no doubt influences the work of the heart in obesity. The heavy deposit of subcutaneous fat acts as a poor con-

³ Fatty infiltration is not synonymous with fatty degeneration. The latter lesion is an intracellular lesion as opposed to an intermuscular deposition of adipose tissue, and is usually of toxic origin.

ductor of heat which decreases the capacity for heat elimination. To compensate, fat people perspire profusely. This leads to excessive ingestion of fluid resulting in increased blood volume, increased venous return and increased work of the heart. This explanation obviously also necessitates a time factor.

The heart in obesity may also be affected indirectly through the effect upon the respiratory organs. Prodger and Dennig (47) and Bowen (48) found the vital capacity diminished; the latter in some instances, found it 20 per cent below normal. Furthermore, Prodger and Dennig, found the respiratory minute volume increased during exercise, the respiratory rate was increased in the sitting position and an increased oxygen consumption during exercise. Directly, these factors are responsible for the dyspnoea. They also confirmed Lichtwitz's (49) finding of an increase in lactic acid in the blood, suggesting that even in the early stages of obesity, there is already beginning circulatory insufficiency.

Clinically, it is well known that obesity aggravates the prognosis of any cardiac disorders, no matter of what origin.

Summarizing, there are a host of factors, given time, that may cause grave myocardial insufficiency in obesity, independent of hypertension or coronary disease.

Relation of obesity to cholelithiasis. That obesity predisposes to cholelithiasis is well known and the stones are usually of the cholesterol type. The reasons therefore are concerned in the problem of the pathogenesis of gall stones in general. There is probably some disturbance in the metabolism of cholesterol, although the blood cholesterol is usually within the range of normal in obesity. [Bruch (50), Bruger and Poindexter (51)]. Nor is the content influenced by a low calory diet. In all likelihood, the stagnation of the biliary contents by lack of exercise, which as Winkelstein (52) has shown tends to propel the bile from the gall bladder, is a contributing factor.

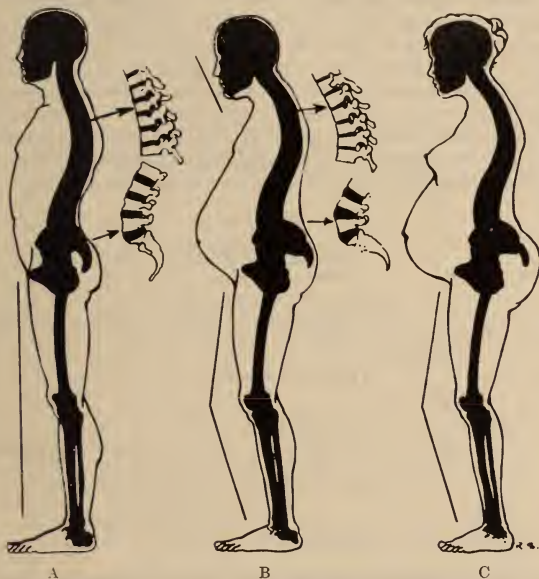
The effect of obesity upon the skeleton. That the increased weight must handicap the mechanics of the skeletal structure is obvious, not only through the effect of the sheer weight itself but through its distributions. The center of gravity is changed, and as a consequence, the lumbar curve of the vertebra first becomes lordotic; this is followed by a compensatory thoracic kyphosis and eventually a cervical lordosis producing a forward position of the head. These changes Kerr and Lagen (53) call the "postural syndrome" and is well represented in figure 1. Kerr and Lagen explain the emphysema that so often accompanies obesity as compensatory to thoracic kyphosis and the consequent flaring of the ribs.

There are a number of other consequences of an orthopedic variety.

The frequency of flat feet in obese patients is familiar.

One of the commonest disturbances is a bilateral arthritis limited to both knees and sometimes the ankles. This is particularly common in stout elderly women. That this form of arthritis is due to weight bearing is proven by its alleviation when a considerable loss in weight is attained. In the early stages, before morbid anatomical changes in the knees have taken place, such an arthritis is even completely curable.

Some years ago, I (54) called attention to a fairly common inflammation of the sartorius bursa that sometimes follows a long continued obesity, especially in women. It is always bilateral and characterized by tenderness over the inner aspect of the tibial condyle, exactly at the site of the conjoined tendon while motion at the knee joint is perfectly free and painless. The history is rather



Types of posture showing effects on spine

- A. Posture, spinal curves and intervertebral discs normal.
 B. Relaxed posture with accentuated spinal curves resulting from a pendulous abdomen.
 C. Postural changes late in pregnancy, similar to those in B, but which never persist long enough to affect the intervertebral discs.

FIG. 1

From *Annals of Internal Medicine*, 10, 569, 1936, Kerr and Lagen

characteristic; the pain only arises when going up or down steps, never when walking on level ground.

*Effect of obesity upon the gonads.*⁴ Obesity in women frequently is preceded or accompanied by amenorrhea. The basal metabolism of these patients usually is normal. The uterus shows involution and flabby musculature. Hormonal studies of the blood and urine are too variable to be conclu-

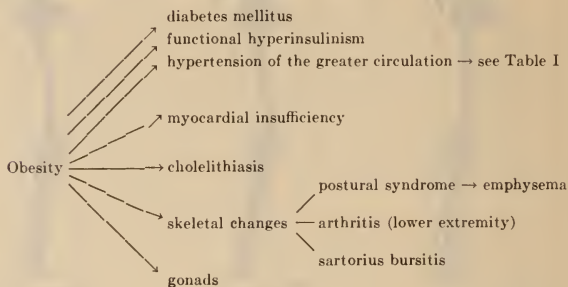
⁴ This section I am indebted to my friend and colleague, Robert T. Frank, M.D.

sive. The same applies to uterine biopsies and vaginal smears. The condition is regarded as functional hypo-ovarianism, but this concept is loosely drawn and not based upon convincing anatomical or other evidence.

Reduction in weight by slow continuous diet commonly leads to reestablishment of menstruation after the weight is reduced. Recurrence of the amenorrhea commonly follows regaining of weight. On the other hand, it should be remembered that occasionally very fat patients menstruate normally or suffer from menorrhagia. Amenorrhea almost invariably is accompanied by sterility.

The simultaneous development of hirsutism and obesity indicates a more persistent type. Gradual and smooth transition to the typical adrenocortical syndrome with moon face, pink striae and osteoporosis has been observed. Many of the intermediate groups show neither chemical nor x-ray changes sufficient to warrant an exact diagnosis. Occasionally pituitary disease simulates the less grave affections (erosion of the sella, ocular symptoms, hypoglycemia).

TABLE VI

The Biology of Obesity

In the male, obesity rarely produces clear cut gonadal symptoms. Diminution in libido may be complained of but no data as to change in sperm count are available.

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ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents. R. OTTENBERG and R. SPIEGEL. *Medicine*, 22: 1, February, 1943. [The abstract appeared in full in the preceding number of this Journal (Vol. 11, p, 315, 1945).]

Clinical Use of Succinyl Sulfathiazole. B. B. CROHN. *Gastroenterol.*, 1: 2, 140, February, 1943.

It is apparent that succinyl sulfathiazole alone used as a specific drug will hardly equal or surpass the 74 per cent improvement found with the use of various measures in colitis, but in Crohn's small series, five cases show an apparent and quick symptomatic cure and eleven more of the series of twenty-eight cases show definite improvement, particularly since the drug exhibits practically no toxic by-effects and can be pushed in large doses with relative impunity. The best results are seen with the handling of cases of acute colitis. If the disease were to be recognized in its early acute stages and treated with succinyl sulfathiazole, the whole picture of lingering debilitating chronic ulcerative colitis might be altered. The favorable effect of the drug in patients bearing fecal fistulae to the abdominal wall is also stressed.

Factors Concerned in the Abnormal Distribution of Barium in the Small Bowel. M. L. SUSSMAN. *Radiology*, 40: 2, 128, February, 1943.

1. The term "deficiency pattern" has been used loosely to designate the roentgen appearance of the small bowel when there is segmentation with changes in motility, tone, and mucosal pattern. There is no definite reason, at the present time, to assume that these findings are necessarily variations of a single pattern with a common pathogenesis.

2. Edema and infiltration of the submucosa, atrophy of the mucosa, muscle damage, and nerve degeneration, modified at times by abnormal bowel content and by unusual hormonal or nervous stimuli, individually are sufficient to produce the "deficiency pattern." In some diseases, such as granulomatous jejuno-ileitis and allergic enteritis, there is no reason to suspect that any other factors are operating.

3. In nutritional deficiency, although the local inflammatory changes are sufficient to produce the abnormal small bowel pattern, a primary tissue disturbance may be produced by the deficiency and, as a result, interference with the normal intestinal reflexes. However, the pathway or tissue through which these deficiencies may operate to produce the small bowel abnormalities remains undetermined.

4. There is experimental evidence which suggests that the pattern can be produced by deficiency in certain vitamin B components. There is no established proof concerning which components are lacking either in experimental or human disease.

On Headaches. J. BERBERICH. *Eye, Ear, Nose and Throat Monthly*, February, 1943.

Studies of headache in patients with sinus diseases and experiments on the dura of the three fossae during skull operations would indicate that every headache, with the exception of neuralgic and referred pains, is always of dural origin. This dural pain can be produced:

1. By direct irritation of the nerves in the dura (brain tumors, extradural tumors, meningeal tumors, extra- and subdural abscess, cholesteatoma, circumscribed inflammation of the dura, etc.) or

2. By circumscribed or generalized increase in cerebrospinal fluid with increased tension of the dura and subsequent pressure on the dural nerves (acute and chronic meningitis, infectious diseases, alcohol, nicotine, eating of ice, migraine, emotions, etc.). Anatomical studies of the sensory nerve supply support this opinion. Sensory fibers are found only in certain parts of the dura, characteristically distributed, in the neighborhood of some arteries and in the choroid plexus; the brain itself is insensitive. From the dura the stimulus travels centripetally via various fibers of the trigeminal, glossopharyngeal or hypoglossal nerves to the nuclei of the medulla oblongata and from there through the lemniscus tract to the thalamus, where it is perceived as pain.

Tuberculous Endobronchitis and Upper Lobe Bronchiectasis. A. H. AUFSES. J. Thoracic Surg., 12: 285, February, 1943.

The etiology of upper lobe bronchiectasis is discussed. The suggestion is made that the bronchiectasis complicating pulmonary tuberculosis may be due in part to bronchial stenosis caused by tuberculous endobronchitis. One case is reported in which, under observation, a tuberculous endobronchial lesion resulted in stenosis followed by bronchiectasis and suppurative of the upper lobe without gross parenchymal tuberculosis. Serial x-ray examination shows the course of the disease from a negative x-ray film to one showing typical bronchiectasis and pulmonary suppurative. Lobectomy was performed with apparent cure.

A Practical Plan for the Treatment of Superficial Fungus Infections. S. M. PECK AND L. SHWARTZ. Public Health Reports, 58: 337, February, 1943.

Accepted methods of the treatment of the various types of dermatophytosis is discussed. The treatment of various types of fungus infections of the skin is given. The fungus infections discussed are both the common and uncommon species encountered. Sixteen formulas are given and the prophylaxis of fungus infections, especially the so-called "athlete's foot" is discussed.

An Outbreak of Microsporon Lanosum Infection from a Kitten. I. BOTVINICK, S. M. PECK AND L. SHWARTZ. Public Health Reports. 58: 317, February, 1943.

A small epidemic of fungus infection of the glabrous skin due to *M. lanosum* was studied. It was of interest to note, in view of the present epidemic of ringworm of the scalp, that in no instance was the scalp affected. The infection could be traced to a kitten in 3 of the cases and to a direct human contact in the 4th case.

The Pretonsillectomy Clinic. B. S. DENZER AND G. FELSHIN. J. Pediat., 22: 239, February, 1943.

Several hundred charts of tonsillectomized children were examined. Most charts were bound in groups and contained only brief notation of the condition of heart and lungs to determine the child's fitness for operation, and not whether tonsillectomy was indicated. Other children had a more or less longer history. 217 children who presented themselves for tonsillectomy were thoroughly studied in the tonsillectomy clinic. Of these, 17 per cent were operated upon after a complete examination. The remaining 180 children fell into the following groups: 1) Allergic conditions, 11 per cent; 2) malocclusion; 3) bad teeth; 4) endocrinological and mental cases; 5) malnutrition; 6) tuberculosis, 15 per cent; 7) other diseases such as worms, anemias, essential glycosuria, syphilis, pediculosis and rickets; 8) normal tonsils referred by lay people; 9) large tonsils in healthy, normal children who have few colds.

Tonsillectomies are not free of fatalities, nor of morbidity. In place of mass tonsillectomies, we should have carefully studied, properly selected cases.

After this study it was recommended to the Hospital that: 1) Permanent tonsillectomy clinic be established as a clearing house for children referred to the Hospital for tonsillectomy; 2) that when children are referred from special clinics, such as the ear, nose, and throat out-patient department, which lack facilities for complete pediatric examination,

such children should be referred to this special tonsillectomy clinic; 3) that this clinic be under the guidance of the pediatric department. A member of the laryngologic staff with the equipment necessary for adequate testing of hearing and nasal, aural, and sinus examination should be associated with the clinic; 4) this clinic should study and evaluate special problems related to tonsillectomy.

The establishment of a pretonsillectomy clinic is a public health venture as well as a clinical problem. It is particularly fitting that pediatric services in Hospitals should take the lead in such public health efforts.

The Stomatitis of Acute Myeloblastic Leukemia. L. STERN AND J. KLAIF. *Ann. Dent.*, 1: 196, March, 1943.

Although the leukemias exhibit protean manifestations in the mouth, a few oral signs occur almost constantly in the acute forms. These consist of hyperplasia of the gums with spontaneous bleeding, followed by a superficial, sloughing ulceration of the mucosae, hypersalivation, and a putrid odor to the breath. As the disease progresses, cervical lymphadenitis, deeper and painful ulcerations, and loosening of the teeth are noted. The teeth and tongue are covered with a tough, dark film of coagulated blood and epithelial elements.

So many of the milder stomatitides resemble Vincent's infection clinically and bacteriologically, that even when the remotest question of diagnosis exists, a blood count is mandatory.

The Stomatitis of Acute Pemphigus Vulgaris. L. STERN AND I. S. COLBY. *Ann. Dent.*, 1: 199, March, 1943.

As oral signs are generally prominent in the early stages of pemphigus, a dental consultation is often sought. The bulla is the characteristic lesion on the mucosa, but moisture, warmth, and bacterial activity in the mouth produces a rapid breakdown, and a variety of clinical pictures develop.

Neither color contrast nor distribution are reliable guides. Pemphigus is suspected, however, if there is a sudden onset of severely painful ulcerations covered with white shreds of desquamating tissue, beginning under the tongue and spreading rapidly to all parts.

A diagnosis of pemphigus is not justified unless (a) other ulcerative disease of the mouth are excluded and (b) confirmatory lesions on the skin are discovered.

Influence of Lecithin Feeding on Fat and Vitamin A Absorption in Man. D. ADLERSBERG AND H. SOBOTKA. *J. Nutrition*, 25: 255, March, 1943.

The fat and vitamin A tolerance tests were adopted for the study of intestinal absorption in cases of sprue. Active sprue is characterized by absence of the usual elevation of the total lipids or of the vitamin A content of the serum following the administration of the test dose of fat or vitamin A, respectively.

Addition of lecithin to the fat and to the vitamin A used in the respective fat and vitamin A tolerance tests enhances the elevation of the total lipids or the vitamin A content of the serum, respectively. This effect is probably due to increased absorption and, perhaps to a lesser extent, to mobilization of hepatic deposits.

Some Clinical Studies on the Psychosomatic Background of Peptic Ulcer. A. WINKELSTEIN AND L. ROTHCHILD. *Am. J. Digest. Dis.*, 10: 99, March 1943.

This study was undertaken to answer a simple question: Given a series of ulcer patients of suitable age and intelligence, is it possible to determine from an ordinary psychiatric interview the existence of psychic conflicts of such a degree as to warrant the assumption that they have some etiologic significance to the ulcer syndrome? The case histories from 34 young adult males with duodenal ulcers served to show characteristic psychic backgrounds. Four strikingly illustrative cases are presented.

The entire group of 33 revealed characteristic psychic backgrounds. They were suffering from chronic frustration and inward direction of repressed, strong emotional stimuli with

strong masochistic and sadistic tendencies. This chronic state of inward tension bore a close relation to the incidence and recurrence of peptic ulcer. These observations point to the strong possibility that peptic ulcer is a psychosomatic disease.

Morphologic Changes in the Rat's Adrenal Cortex Under Various Experimental Conditions.

E. L. SARASON. Arch. Path., 35: 373, March, 1943.

An attempt has been made to correlate morphologic changes in the adrenal cortex of the rat with various experimentally produced metabolic and endocrine disturbances. The continued administration of desoxycorticosterone acetate caused atrophy in the male adrenal but not in the female. The atrophy is characterized by shrinkage of the glomerulosa layer and depletion of lipoids. Reduction in the serum potassium level caused no changes in the adrenal cortex. The adrenal atrophy following hypophysectomy was characterized by an entirely different histological picture from that seen following cortical hormone administration. This would indicate that the atrophy following the latter was not mediated through the pituitary. Castration of adult female rats caused no atrophy of the adrenals. Acute inanition resulted in adrenal hypertrophy more marked in the female. Chronic inanition in hypophysectomized animals resulted in greater atrophy than that seen in well-nourished hypophysectomized animals. This would indicate that factors other than the lack of adrenotropic hormone may be responsible for the adrenal atrophy seen in chronic inanition.

Late Invasion of Bladder and Prostate in Cancer of the Rectum or Rectosigmoid following Abdomino-perineal Resection. G. D. OPPENHEIMER. Ann. Surg., 117: 456 March, 1943.

Nine instances of late invasion of the bladder and/or prostate and seminal vesicles following abdomino-perineal resection for cancer of the rectum or recto-sigmoid were studied and the management of these cases is described. One of these patients was helped remarkably by radiotherapy and transurethral resection. He is alive nine years after abdomino-perineal resection and two years after treatment of the cancerous infiltration of the prostate.

The sequelae following urologic extension of rectal cancer, both to the upper and lower urinary tracts, occur more frequently than was formerly realized. The postmortem findings of 50 patients with rectal cancer were summarized to illustrate this point.

Clinical Differential Demonstration of Uterine and Tubal Contractions by Kymographic Uterotubal Insufflation. J. C. RUBIN. Am. J. Obst. & Gynec., 45, 419, March, 1943.

Recent clinical observations and experimental work on living and surviving genital organs of the rabbit by means of kymographic uterotubal insufflation have confirmed earlier conclusions. The kymograph tracings of manometric oscillations observed during uterotubal insufflation represent rhythmic tubal contractions and relaxations. They are not due to changes in tonicity *per se* but to actual contractions whose rate varies per minute in accordance most probably with the particular phase of the ovulation menstruation cycle. The non-pregnant uterus has been demonstrated to exhibit a contraction-relaxation phenomenon under suitable distention and recorded by appropriate manometric devices. The character of the contractions differs in each organ, the uterus in general undergoing slower motions of much shallower force. The pressure medium in the uterus may be solutions, gas or air without balloon enclosure and with an intrauterine balloon. The ideal pressure medium within the lumen of the tubes has been found to be CO₂ gas which is insufflated at a constant rate of flow. Salt solution or other fluid injected through the tubes under a constant pressure rate flow has been found unsuited in comparison with CO₂ in the present setup for the recording of pressure oscillations emanating from the tubes. Adoption of aneroid manometers and a photoelectric recorder has helped in establishing the difference in pattern between tubal and uterine contractions in the same and different cases.

BOOK REVIEW

Clinical Evaluation of the Rehabilitation of the Tuberculous. Experience at Altro Work Shops 1915-1939. LOUIS E. SILTZBACH: Report of the Committee for the Care of the Jewish Tuberculous, Inc. Pp. x-70, with 33 tables, Published by the National Tuberculosis Association, 1790 Broadway, New York 19, N. Y., 1944.

This monograph on rehabilitation of the tuberculous is based on a study of 964 ex-patients with pulmonary tuberculosis admitted to a medically controlled garment factory, the Altro Work Shops, between the years 1915 and 1939. The follow-up medical observation upon which this report is based extended in some cases over a period of 25 years, and 92 per cent of the cases were traced 10 years.

In this publication Siltzbach presents an objective and scholarly study of the problem of rehabilitation, and of the results observed, from many angles. With the aid of numerous tables and graphs he brings into focus the various aspects of the subject. Among the topics discussed and illustrated are the following: the medical status of workers on admission, including previous sanatorium experience, stage of the disease, clinical status and sputum history; analysis of experience with workers during their Altro stay, including work dosage, non-tuberculous illness, length of work course, follow-up examination after discharge, occupation after discharge; survival rates and mortality of Altro workers, according to stage of disease on admission, sputum history, etc.

There is an interesting comparison of the medical status of the workers in the two periods of the Altro's history, 1915-1929 and 1930-1939. During the latter period, earlier diagnosis and more effective treatment simplified the problem of rehabilitation and netted more gratifying results. Thus the author emphasizes the fact that the antituberculosis program is a tripartite scheme in which the rehabilitation portion is intimately bound to case finding and treatment. The value of the latter two portions of the program is now universally recognized. The equal importance of rehabilitation in the antituberculosis scheme is not so widely appreciated.

In this admirable report Doctor Siltzbach convincingly demonstrates the value of rehabilitation as carried out in one project The Altro Work Shops. This publication is the first authoritative study on the important subject of rehabilitation of the Tuberculous, and well worth reading by all interested in the problem of tuberculosis.

H. HENNEL, M.D.

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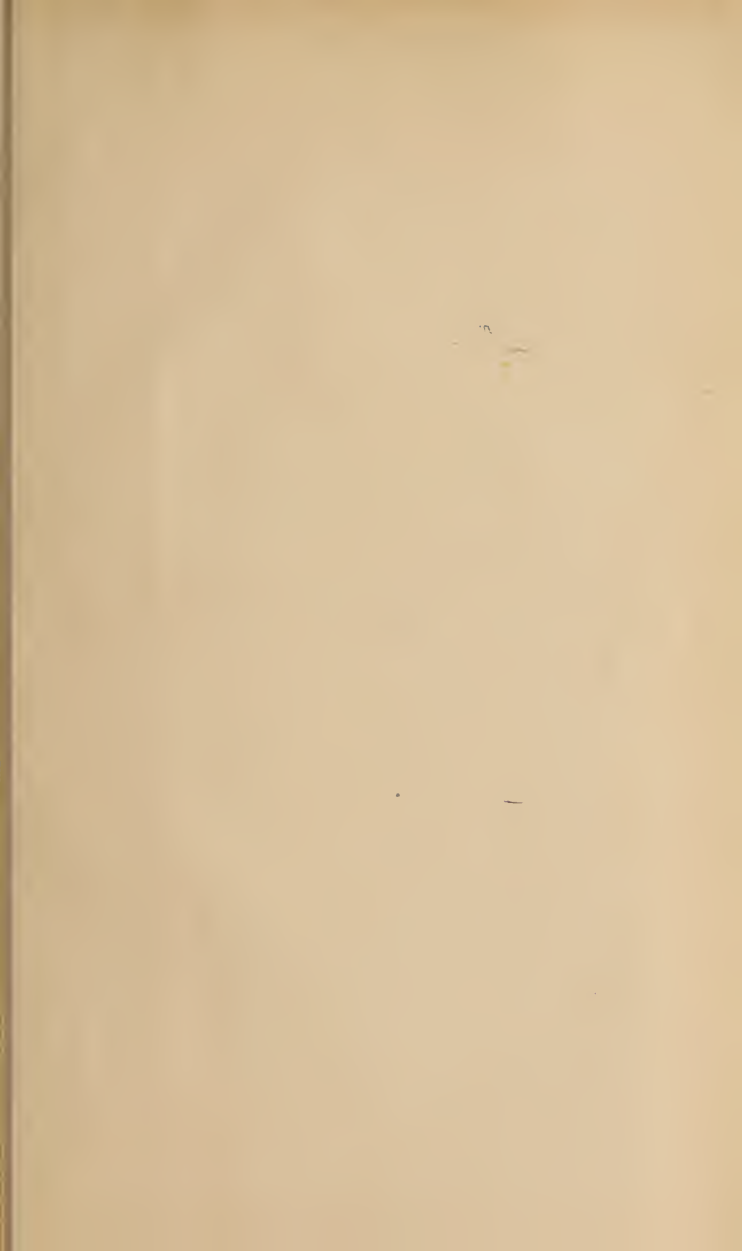
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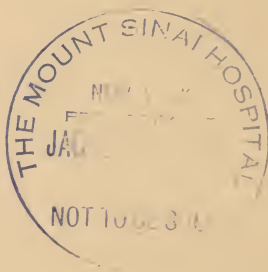
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